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MALARIA, INFLUENZA AND DENGUE

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EDITORIAL SUPERVISION OF

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PREFACE.

THE excellence of the series of monographs issued under the editorship of Professor Nothnagel has been recognized by all who are sufficiently familiar with German to read these works, and the series has found a not inconsiderable proportion of its distribution in this and other English-speaking countries. I have so often heard regret expressed by those whose lack of familiarity with German kept these works beyond their reach, that I was glad of the opportunity to assist in the bringing out of an English edition. It was especially gratifying to find that the prominent specialists who were invited to co-operate by editing separate volumes were as interested as myself in the matter of publication of an English edition. These editors have been requested to make such additions to the original articles as seem necessary to them to bring the articles fully up to date and at the same time to adapt them thoroughly to the American or English reader. The names of the editors alone suffice to assure the profession that in the additions there will be preserved the same high standard of excellence that has been so conspicuous a feature in the original German articles.

In all cases the German author has been consulted with regard to the publication of this edition of his work, and has given specific consent. In one case only it was unfortunately necessary to substitute for the translation of the German article an entirely new one by an American author, on account of a previous arrangement of the German author to issue a translation of his article separately from this series. With this exception the Nothnagel series will be presented intact.

ALFRED STENGEL.

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EDITOR'S PREFACE.

My duties as editor of this volume have been in one respect slight, in another more arduous. For, on the one hand, I have thought it best to leave almost unchanged Prof. Mannaberg's very comprehensive and learned treatment of the history, symptoms, and treatment of malaria. The only changes I have made in his article have been to correct the views and arguments based on the miasmatic theory of the origin of malarial infection which the discovery of the part played by certain mosquitos in transmitting infection has rendered untenable. I have inserted a few details recently added to our knowledge, of that still not fully understood exhibition of malarial infection, viz.: malarial hemoglobinuria, or blackwater fever. I would insist here on the necessity of complete analyses of the urine in such cases. To mention only one point: it is important to determine how quinin is excreted, for if, as has been recently stated, quinin is not eliminated in the urine *during* the actual hemoglobinuric attack, but only subsequently, this would guide a physician in practice as to the all-important question which he finds so difficult to answer, Shall I give quinin or not?

Regarding "malarial cachexia" we are in a transition period, for while many of these cases are due to a distinct parasite (*Leishmania donovani*), yet in many, it appears from the most recent work, it is impossible to find these.

I have further added a short note on the Romanowsky-Ziemann stain, the best of all stains for the malarial parasites, giving a practical and certain method of preparing it—leaving out of account the numerous elaborate modifications which in my experience have no advantage over the simple method given.

On the other hand, my duties have been more arduous in writing an account of the mosquito-malaria question in all its manifold bearings. I have endeavored to give a concise but brief account of all the important facts now known to us. The task has been made easier by the fact that since the discovery of the development of the malaria parasites in the mosquito no fundamental change has been made in our original knowledge. In one important respect this has been extended by the discovery of the part played by the native populations of tropical regions in disseminating the disease. The great fact is now fully recognized that the native (children) population is an ever-present and extremely dangerous source of infection, and the origin of malaria among Europeans is completely explained.

Finally, the main methods of prophylaxis have been indicated. Already progress has been made in the anti-malaria campaign, and I shall not have contributed this portion in vain if I have conveyed to the physician the necessity, having regard to prophylaxis, for a study not only of malaria but also of mosquitos and their habits.

J. W. W. STEPHENS, M.D. CANTAB. D. P. H.

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MALARIAL DISEASES

BY

DR. JULIUS MANNABERG

MALARIAL DISEASES.

GENERAL PART.

HISTORY.

The existence of malaria in the ancient times is proved from the chronicles of contemporaneous writers. It appears, moreover, likely that the disease extends to the infancy of the human race, for it is in our day unquestionable that cultivation—especially cultivation of the ground—and malaria are two factors that flourish counter to each other, inasmuch as where husbandry does not exist, malaria is luxuriant, and where the soil is tilled, malaria diminishes and even disappears.

According to W. Groff, malaria was well known to the ancient Egyptians. The word "Aat," occurring among others in the inscriptions on the temple at Denderah, is said to indicate the annual recurring epidemic.

The history of our knowledge of malaria is divided into three epochs by two principal discoveries: the first, the recognition of the specific action of cinchona bark; the second, the demonstration of the malarial parasites by Laveran.

Previous to the discovery of Peruvian bark and its introduction into therapy, malaria was, with other fevers, thrown into a confused conglomeration. Its separation from this confusion was brought about by the effects of the bark, though it was only in our own century that the classification was made absolute. This classification was the result of clinical observation, and especially the study of pathologic anatomy.

Though we may allow, without further discussion, that the ancients had no very clear ideas as to the differentiation of different fevers, it is not true that such a differentiation was not anticipated and earnestly sought. The writings of Hippocrates and Celsus show that they had pretty correct notions as to whether or not a certain fever would terminate favorably, as to the origin of the fever, and as to the causal connection of the fever with its results.

Hippocrates[*] classifies fevers "without evident pain" (therefore without distinct localization of the symptoms) exactly as we do. He writes[†]: "Omitting those arising with evident pain, there are four types, the names of which are: continued fever, quotidian fever, tertian fever, and quartan fever." That the distribution of fevers over different seasons was remarked by Hippocrates is shown by the following quotations: "Of summer, certain of these (already mentioned), and continued, ardent, and tertian fevers," etc.; further: "Of autumn, most of the summer, quartan, and irregular fevers, enlarged spleen, dropsy," etc.[‡]

No one would fail to recognize that his irregular fevers refer to relapsing fevers, his enlarged spleen and dropsy, to malarial cachexia.

That Hippocrates appreciated the causal connection between fever and cachexia is evident from many expressions like the following: "This disease is habitual to them both in summer and in winter, and in addition they are very subject to dropsies of a most fatal character; and in summer dysenteries, diarrheas, and protracted quartan fevers seize them, and these diseases, when prolonged, dispose such constitutions to dropsies, and thus prove fatal.[§] Or: "Convalescents (therefrom) will pass into quartans, and from quartans into dropsies."[‖]

The favorable influence of humidity on fever is shown by: "But if the winter be dry and northerly, and the spring showery and southerly, the summer will necessarily be of a febrile character."[**]

In relation to marsh land and the dwellers thereon he writes: "As to the inhabitants of Phasis, their country is fenny, warm, humid, and wooded; copious and severe rains occur there at all seasons; and the life of the inhabitants is spent among the fens, for their dwellings are constructed of wood and reeds and are erected amidst the waters. For these reasons the Phasians have shapes different from those of all other men; for they are large in stature and of very gross habit of body, so that not a joint or vein is visible. In color they are sallow, as if affected with jaundice. Of all men, they have the roughest voices."[††]

Hippocrates attributes the origin of the fever to the drinking of contaminated water: "For water contributes much towards health. Such waters then as are marshy, stagnant, and belong to lakes are necessarily hot in summer, thick, and have a strong smell, since they have no current; those who drink them have large and obstructed spleens. . . " (chap. vii).*

---

[*] Hippocrates, "Sämmtliche Werke," Uebersetzung von R. Fuchs, München, by Dr. Lüneberg, 1895. [The English translator has followed the translation of Francis Adams, for the Sydenham Society, except in the first instance quoted from the book on the "Nature of Man," which Adams considered spurious.—Ed.]

[†] "Nature of Man," chap. xvi.

[‡] "Aphorisms," sect. iii, 21 and 22.

[§] "Airs, Waters, and Places," chap. viii.

[‖] *Ibid.*, chap. x.

[**] *Ibid.*, chap. x.

[††] *Ibid.*, chap. xx.

Celsus has left us a finished clinical description of intermittent fever and many of its accompanying symptoms. He differentiates a quotidian fever, composed of quartan attacks, and mentions as an especially pernicious fever the malignant tertian (then called ἡμιτριταιον).

That the Romans were very close to the trail in regard to the etiology of malaria is proved from the writings of Varro, Columella, Palladius, Vitruvius, and Avicenna, who made swamps, the emanations from them, and the minute animals living in them, responsible for the disease. This etiologic idea was lost in the middle ages on account of the influence of Galen's teaching, and Morton, at the end of the seventeenth century, was the first again to pick up the thread.†

Mercatus, the court physician to Philips II and III, gives a description of pernicious cases occurring in connection with intermittent fever, and says that they were associated especially with the tertian type. In general, this author is so deeply involved in the humoral pathologic vagaries that pervaded medicine at his time as to be almost totally unintelligible to us.

The Arab physicians also, as Rhazes, Ebn Sina, were acquainted with intermittent fever.

The second epoch began with the introduction of Peruvian bark —the middle of the seventeenth century. Following its opening, in quick succession, came the memorable treatises of Morton, Torti, and Sydenham. The complete clinical pathology of malaria stands out fully developed in the first two especially.

With cinchona in their hands, Torti and Morton divided the "essential fevers" into two principal groups—namely, those that were curable by it, and those in which it had no effect. On the basis of this differentiation Torti built up a description of malarial diseases that must always remain classic. In a clinical way his work has been surpassed by no subsequent writer, and will very probably never be surpassed. Acuteness of observation, wealth of experience, facility of exposition, are the factors that go to make its prominence.

---

* Bellos (Athens) declares there is a complete identity between the fevers described by Hippocrates and those occurring to-day in Greece.

† The goddess of fever (Mefitis) had a temple on the Capitol. She was represented as an emaciated, half-nude, bald-headed, horrid figure, with a huge belly and swollen veins. That malaria played a rôle in public affairs at the time of the empire is evident from Horace's letter to Mæcenas ("Epistolarum," lib. i, ep. 7, vi ad Mæcenam). Horace begs Mæcenas to extend his leave of absence, so as to permit him to remain away during the intensest of the summer heat, for when the first figs ripen and faces become pallid from fever, the chief of the funeral pomps (designator), with his black assistants, is very active, and the reading of wills becomes the order of the day (Jilek).

We will often discuss Torti's views in the following pages, and will, therefore, refrain from repeating them now.

Morton's highly interesting book contains, besides a broad discussion of the action of quinin based on a large experience, the first germ of an etiologic idea since Galen's time.

The notion of a connection between the condition of the ground and the meteorologic and climatic conditions and malaria was introduced and popularized especially by Lancisi. He was, moreover, the first who endeavored to demonstrate this question experimentally; and, likewise, the first to remark the strikingly dark color of the liver in fatal cases of malaria.

An acquisition to the subject in the eighteenth century that is worthy of mention was de Haen's demonstration of the rise of temperature during the chill.

It was owing to the progressive colonization, during the eighteenth century, of the various parts of the world outside of Europe that a knowledge of the wide geographic distribution of malarial diseases was acquired (Lind, Pringle), though with it came new difficulties in the differentiation of malaria from other endemic tropical diseases, as yellow fever. The separation of these was the work of pathologic investigation in the nineteenth century.

On one hand, the pigmentation of the organs and the blood of malarial cases had become more and more striking (Bailly, Folchi); on the other, the characteristic lesions of that disease most difficult to differentiate from malaria, namely, typhoid fever, were found in the small intestine by Prost, Bretonneau, Louis, Gerhard, and Pennock.

An important epoch in the history of malaria was introduced by Heinrich Meckel's discovery (1847) of the pigment and the pigmented corpuscles. This discovery was made possible by the work of Virchow, Heschl, Planer, and Frerichs. Yet we must not forget the clinical work of Maillot, Haspel, Léon Colin, Griesinger, Le Roy de Méricourt, Bérenger-Féraud, Corre, Morehead, Fayrer, Baccelli, Tomaselli, Karamitsas, and Hertz in the rearrangement of the new material, nor that of Kelsch and Kiener, based on recently discovered facts. All added a wealth of clinical and anatomic knowledge to the subject.

Simultaneously, every effort was made to solve the etiology. After many futile endeavors to find the disease excitant, the existence of which had long been surmised (Mitchell, Salisbury, Eklund, Tommasi-Crudeli, and others), Laveran succeeded, in November, 1880. Several years of skepticism followed, but eventually Laveran's discovery, which opened up the third epoch of malarial investigation, conquered the medical world. There is scarcely a known malarial focus on the earth where this discovery has not been confirmed. A large number of investigators at once took up the study of the development of the disease from this point of view, though, remarkable to say, the greatest number of these were found among the Italians and the fewest among the compatriots of the discoverer. Some of the names that must be mentioned in this regard are Golgi, Marchiafava, Celli, Grassi, Feletti, Bignami, Bastianelli, Romanowsky, Di Mattei, Osler, Thayer, Hewetson, Manson, Sakharoff, and Metschnikoff.

To this time also belongs the discovery of Gerhardt that malaria could be transmitted by the inoculation of the blood of a patient. Nor should we fail to mention the discovery of quinin by Pelletier and Caventou (1820).

GEOGRAPHIC DISTRIBUTION.

Malaria is one of the most widely distributed infectious diseases; yet its distribution is by no means uniform, for it is most prevalent in the region of the equator and gradually diminishes toward the north and south. The most northerly point at which malaria has been observed is, as far as we have any knowledge, Brahestad (64° 41′ N. L.), in Finland. Here, in 1861, Hjelt reported intermittent fever, though, as was to be expected, with only occasional epidemic spread. According to Hirsch, the isotherm from 15° to 16° indicates the confines within which the disease is always seen.*

Malaria flourishes in infected regions as an annual recurring disease of greater or less severity. Sometimes, however, it oversteps its usual boundaries, assumes an epidemic or pandemic character, and spreads to territories that are otherwise exempt.

Within historic times the distribution of malaria has experienced important changes. Entire countries that were once severely afflicted are now without a case, and vice versâ.

At the beginning of this century Holland showed an endemicity that stood qualitatively and quantitatively scarcely behind that of the present Agra Romana. This is now limited to a relatively small focus, and no longer presents anything like the malignity of earlier times. From the comparison of the reports of Sydenham and Morton with the evidence of the present day, the same is true of London, as well as of England and Ireland.

In France, the regions of Rochefort, the banks of the Loire, the mouth of the Gironde, of the Adour, etc.; in Germany, the regions of the Harz Mountains, Augsburg, and Würtemberg, are now almost immune, though they were in the past dangerous foci.

In Austria-Hungary, also, numerous malarial foci have disappeared. Vienna, Prague, Komorn not uncommonly showed fatal cases of malaria, even up to the middle of the nineteenth century, while such occurrences are now very rare.

On the other hand, malaria is continually making new conquests in other countries. Italy is such an example from olden times; the

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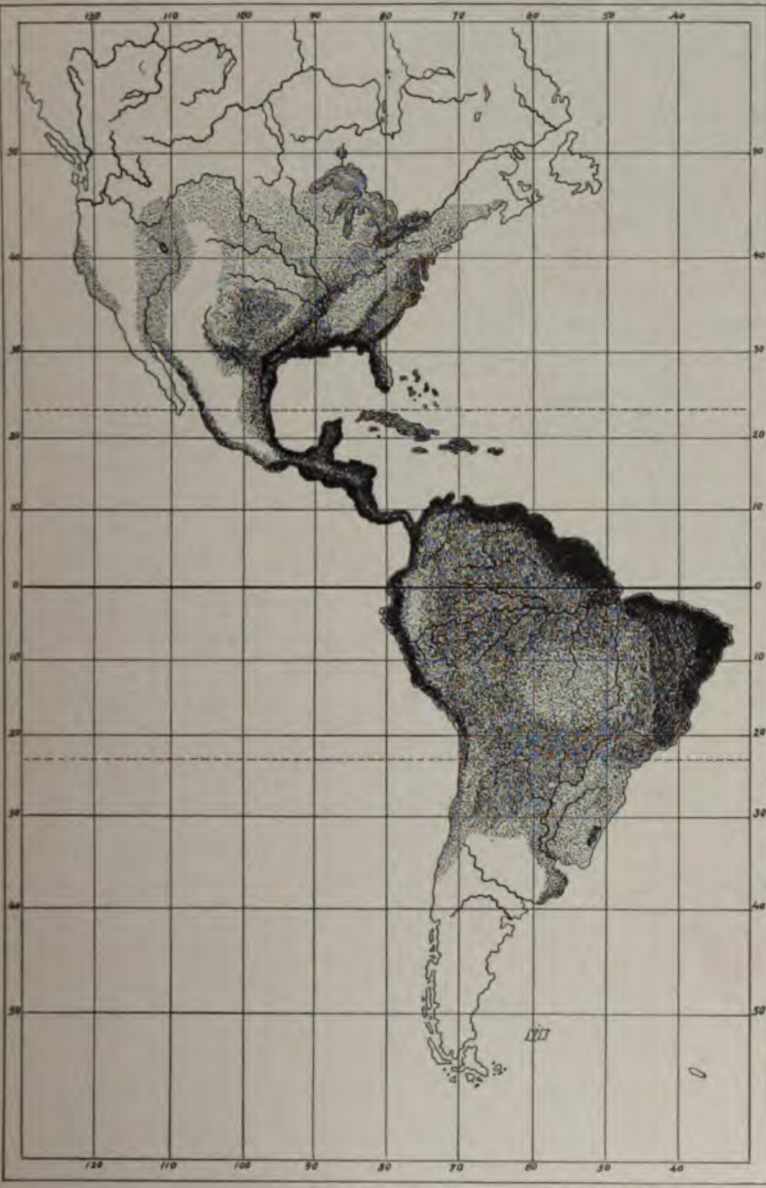
* Places with a mean summer temperature of 15° to 16°.

PLATE I.



Showing the distribution of malaria as indicated by the intensity of the shading.

islands of Mauritius and Réunion, numerous places in North America, Chile, and in a lesser degree Sweden are recent examples.

The most important foci of malaria to be found at present are the following*:

Africa shows its worst malarial foci in the tropical regions. On the west, the whole coast from Sénégal to Kongo is the home of severe forms. Of the islands along this coast, Fernando Po and St. Thomas are infected, and St. Helena free. From Kongo downward, on the whole, the foci decrease in extent and the disease in severity. Yet in German Southwest Africa intense malaria also occurs. Cape Colony is practically exempt.

In the southeast the islands of Madagascar, Mayotta (Comoro), Nossi Bé, La Réunion, and Mauritius represent also intense malarial foci. The coast itself, from Delagoa bay to Zanzibar, is intensely infected. The west coast of the Red Sea is, with the exception of a few places (as the prolific Massawa), but little contaminated.

Somaliland and Abyssinia, especially in their mountainous districts, are pretty well spared, though between Abyssinia and the Chad swamp an immense malarial region stretches into the interior, including Nubia, the lowlands of Kordofan and Darfur (therefore a great part of the Sudan).

Upper and central Egypt manifest the disease but seldom, though the region of the Nile Delta, beginning at the province of Fayum, is here and there infected.

In northern Africa the disease is especially endemic in Algeria. We may name especially in the province of Algiers, the Alloulah Lake and the banks of the Chiffa; in the province of Oran, the plains of Sig and Habra; in the province of Constantine, the plains of Seybouse and Lake Fezzara. The conditions in Algeria have decidedly improved under French rule, as is evident from the army sanitary reports. In former years the morbidity from malaria in the Algerian garrison amounted to 48 per cent. of the whole force. In late years (quoted from Laveran):

In 1890 malaria morbidity	146.00	per cent.
" " " mortality	1.50	" "

Fifty-eight of the deaths were due to pernicious attacks; 43 to cachexia; 21 to remittent fever, making 112 in all.

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* We have taken our data especially from Hirsch, to whose excellent work we refer the student for further details.

In 1893	malaria	morbidity	84.06	per cent.
" "	"	mortality	1.71	" "
In 1894	"	morbidity	99.30	" "
" "	"	mortality	1.03	" "

Some of the oases of the Great Desert, as Biskra, Tuggurt, Ouaregla, are also infected, thus making a continuation of the foci in the Sudan.

In Tripoli and Tunis there are several foci about the interior lakes, oases, etc.

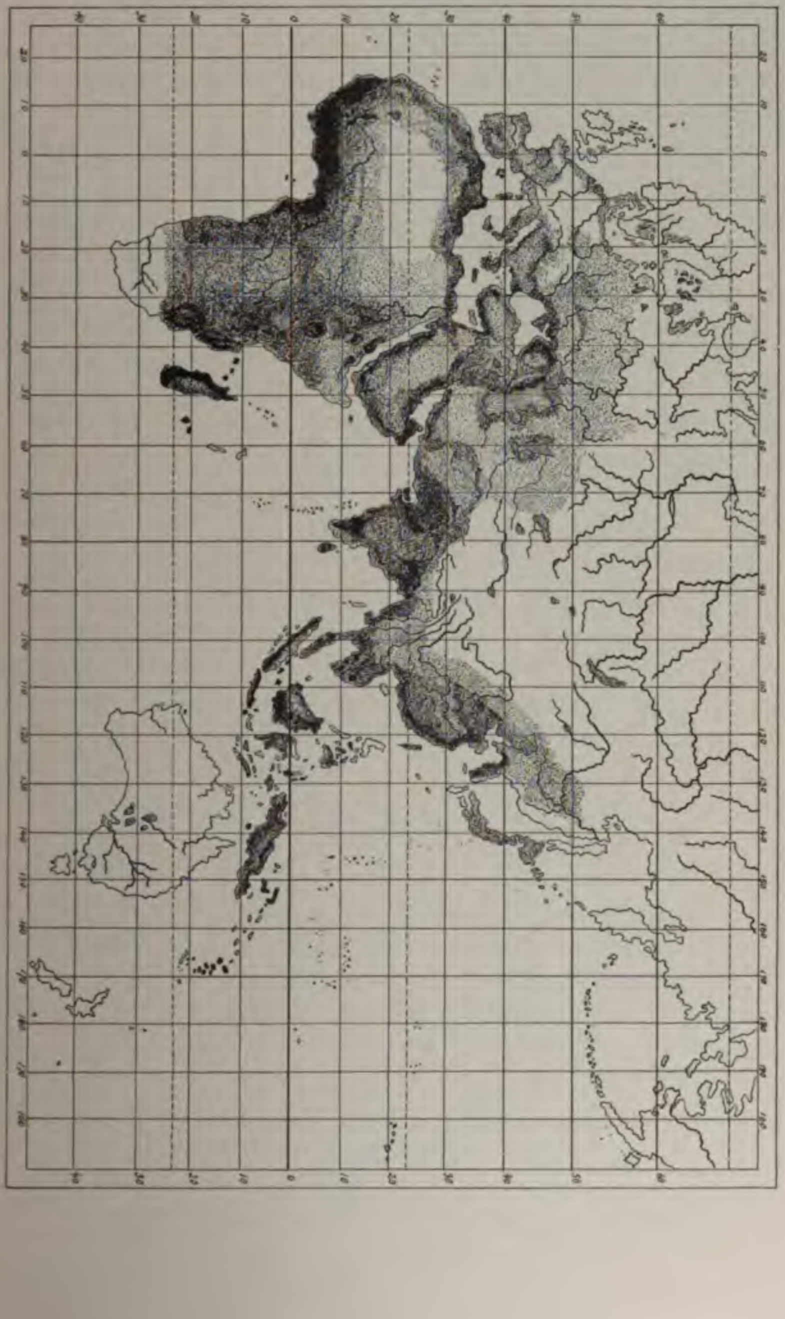
Asia shows foci on the west and south coast of Arabia (especially Muscat), the coast of the Persian gulf, Mesopotamia, the Syrian coast (Palestine), and the banks of the Black Sea, whence the disease extends over the marshy coast of the Caspian Sea to Persia. Hotbeds are also found in Beluchistan and Afghanistan.

India.—The extent to which malaria prevails in India is difficult of determination. Of so little value are Indian statistics, from the way in which the majority are compiled by uninstructed subordinate officials and from the fact that a large, if not the larger, portion of the fevers so classified is not malarial in nature, that we must hesitate in making any very definite statements. With some exceptions malaria does not attain in India that intensity it does in tropical Africa, and whereas in Africa the malignant tertian parasite gives its stamp to the character of the fevers, in India it is the simple tertian parasite that prevails. The Terai, at the foot of the eastern Himalayas, undoubtedly, even to the present day, merits the ill-fame attached to its name, and as we pass from here into Assam, we still find foci of severe malaria and malarial hemoglobinuria. In the hill regions of Madras malaria may also occur with equal intensity, whereas in the plain districts of Madras malaria, though prevalent, is of a much less intensity. Probably along the western Ghats malaria will be found to be intense. Malaria, though widely prevalent elsewhere, yet does not attain the severity of those parts mentioned, and we have not a few towns in India, such as Calcutta and Bombay, where malaria, even in the environs, is almost negligible.

Prominent centers occur in the Malay archipelago, in the Nicobar Islands, Sumatra (especially Singkel), Java (Batavia), Borneo, Celebes, and Amboina (in the Molucca Islands), while the Philippines suffer but little. More or less severe foci are scattered about Siam (especially in the valley of the Menam and Bangkok), Cochin China (along the course of the Mekong), and Tongking.

The coast and interior of *China* (Hong-Kong, Canton, Shanghai)

PLATE II.



Showing the distribution of malaria as indicated by the intensity of the shading.

and the coast of Korea and Manchuria are markedly infected, while Vladivostok is almost free.

In *Japan* the disease occurs for the most part only in a mild form.

Australia.—The Australian continent, as well as most of the islands of Oceanica, is almost exempt from malaria. The only places infected are the coasts of New Guinea (Kaiser Wilhelm's land), Finschhafen, the Solomon Islands, and the Bismarck archipelago. In New Caledonia, in spite of its numerous swamps, malaria is unknown. This is likewise true of Tasmania and New Zealand, the Fiji, Samoan, Sandwich, and Society islands.

America.—Among the Antilles malaria prevails to a greater or less extent, with the exception of Barbados, St. Vincent, and Antigua; while the Bahamas are relatively almost exempt. On the east coast of South America, Guiana is intensely infected.

Regions that suffer greatly and sometimes intensely are found in North Brazil, Paraguay, Bolivia, and Uruguay. Argentine Republic is almost immune.

Foci of endemicity are found on the west coast of Peru, Ecuador, and, since a comparatively recent time, Chile. In Central America and Mexico the Atlantic coast is badly contaminated, while the Pacific coast shows only scattered foci.

The eastern coast of North America, along the Gulf of Mexico, is markedly infected, and here and in the Southern States we find malarial hemoglobinuria (blackwater fever); we find malaria up the Mississippi far into the interior (Arkansas, Indian Territory, Missouri); it is found too in Texas and in a portion of New Mexico, as well as in Florida and Georgia. Of the Middle States, those lying along the east coast (South and North Carolina, Virginia, Maryland) especially show foci, while those lying more centrally and toward the northwest (Ohio, Indiana, Illinois, Missouri, Iowa, Minnesota, Wisconsin, Michigan) are less affected. Foci are also met with in southern Michigan, on the shores of Lake Ontario and Lake Erie, less frequently on the shore of Lake Huron, and almost not at all on Lakes Superior and Michigan.

Pennsylvania and New York show only a few mild centers, especially along the Hudson and Delaware rivers, and these are gradually disappearing with the advance of agriculture.

In Canada, except on the northern shore of Lake Ontario (Kingston), the disease can scarcely be called endemic.

In the Western States malaria is found in Wyoming, Utah, Colorado, Arizona, and California (along the Sacramento and San Joaquin).

Europe.—*Russia.*—A strongly infected region extends "from the steppes to the Caspian Sea, along the Volga, over the Caucasus lowlands and the northern shores of the Black Sea, over Taurida, Crimea, Kherson, Bessarabia, along the course of the Dnieper and Dniester to Ekaterinoslaf, over Ukraine and Volhynia, along the Danube, over the Moldau and Wallachia, through Bulgaria, Hungary, etc." (Hirsch).

Less severe foci are found in Tula, Samara, Kazan, and Novgorod.

The Caucasus is especially rich in malarial centers. These lie principally along the coast of the Black Sea, from Novorossinska to Tchorka, throughout the valleys to the north of the Caucasus, throughout Batum, on the coast of the Caspian Sea, in the lowlands of Koubak and Terek, and certain places in the governments of Elisabethpol and Erivan, in the Transcaspian district, and on the oasis Akal-Tekinski.

Austria-Hungary.—In Galicia many places are infected. The principal foci are found in Cracow, Bosnia, Wadowice, Tarnów, and in the regions of the Dniester, Grodek, Lemberg, Sanok, and Tarnopol.

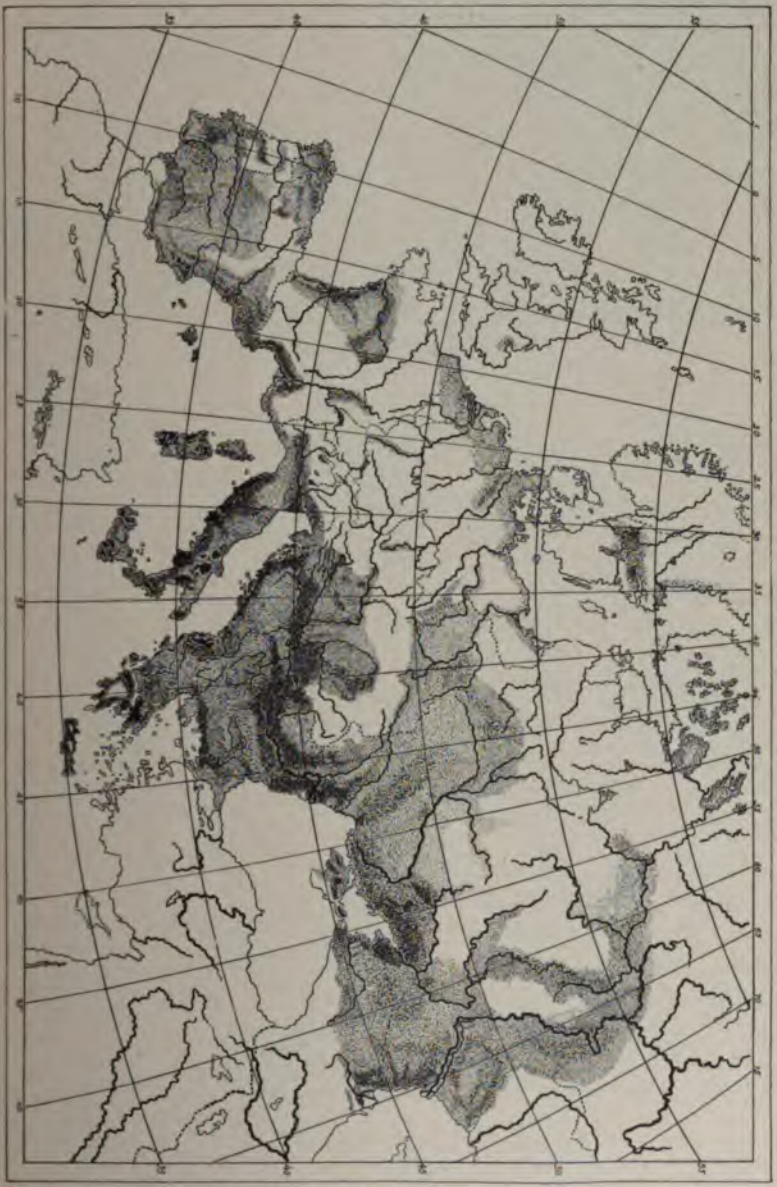
A row of foci is found along the Danube and its tributaries. These take their origin in the Marchfeld region, follow the small Hungarian lowlands (Schütt, Wieselburg, Komorn, Raab), then the great Hungarian lowlands between the Danube and Theiss (the counties Tolna, Baranya, Bács-Bodrog, Torontál, Arad, Temes, Csanád, Békés, Szolnok), and wind up between the Save and Drave (in the province of Slavonia and Croatia) and on the right bank of the Save in Bosnia.

On the Adriatic portions of the Istrian and Dalmatian coast several islands are infected. Hotbeds are found in the Narenta valley (Metkovic) in Dalmatia, and in Pola in Istria, though this latter shows a decline since the improvement of the soil has been taken up. Bosnia and Herzegovina show along the Bosna and Narenta numerous foci.

According to Myrdacz, the yearly average of malaria cases in the Austro-Hungarian army from 1870 to 1882 amounted to 55,154, or 211.3 per cent. of the average force. In individual years considerable fluctuations were observed, as in 1870, 171.3 per cent.; 1872, 298.7 per cent.; 1882, 133.9 per cent.

"According to the territorial distribution of the military force the cases per 1000 were as follows: in Innsbruch, 25.9; in Prague, 29.9; in Brünn, 43.5; in Vienna, 63.5; in Gratz, 96.6; in Lemberg, 150.6;

PLATE III.



Showing the distribution of malaria as indicated by the intensity of the shading.

in Trieste, 166.4; in Sarajevo (1880–1882), 211.8; in Zara, 246.7; in Cracow, 247.7; in Budapest, 266.8; in Hermannstadt, 277.6; in Pressburg, 284.6; in Kaschau, 306.2; in Temesvár, 473.8; in Agram, 537.3."

In the decennium from 1873 to 1882 there were 72 deaths from acute malaria.

We may mention as especially severely infected the garrisons of Peterwardein-Neusatz, Otocac, Esseg, Hungarian Weisskirchen, Szolnok, Szegedin, Arad, Güns, Kecskemét, Grosswardein.

Since 1882 malaria has shown a steady and striking decrease in the Austro-Hungarian army. The average morbidity of the years 1883–1887 amounted to only 59.1 per cent. (see Myrdacz). Still later we find:

In 1891 a morbidity of	30.6 per cent.
" 1892 " " "	40.4 "
" 1893 " " "	34.7 "
" 1894 " " "	28.0 "
" 1895 " " "	26.1 "
" 1897 " " "	22.6 "

The average yearly morbidity for the years 1870 to 1882 was 211.3 per cent., in contrast to 30.4 per cent. for 1891 to 1897.

The striking diminution of malaria in the army is to be referred in part to the improvement in the sanitary conditions, and in part to an independent decrease in endemicity.

On the *Balkan peninsula*, Albania and the majority of the coast towns of Greece are severely infected; among the islands, Crete, Cephalonia, Santa Maura, and Corfu.

The Apennine peninsula shows principally two great centers, one in the plains of the Po, the other the western coast from Pisa downward. Over the Lombard and Venetian lowlands are scattered mild or moderately severe foci. The worst infected places are the provinces of Novara and Cremona (the region between Pandino and Somino). On the Adriatic coast numerous extensive and severe centers are found in the provinces of Venice, Padua, Rovigo, and Ferrara.

On the west coast of Italy the malarial region begins at the mouth of the Arno and reaches its first high level in the neighborhood of Grosseto (Maremma Toscana), from where, to Civitàvecchia, it lessens in severity. A little southwest from here begins the markedly infected Roman Campagna, which runs into the malarial hotbeds of the Pontine marshes between Velletri and Fondi. Particularly fatal are the surroundings of Sermoneta, Sezze, Roccasecca, Prossedo, and Amaseno. Further south the banks of the Garigliano and Volturno are strongly infected; less so, the vicinity of Naples. To the south of Salerno, in the neighborhood of Paestum, an extensive focus is found, and from here downward numerous smaller more or less severe foci. Yet not alone the coasts of the peninsula, but also the interior of the country, especially the provinces of Molise, Apulia, and Basilicata, and, in a lesser degree, Calabrie, show numerous and sometimes very severe centers (Montefalcone, S. Croce, S. Bartolomeo, in Galdo, Castellucio, S. Mauro, etc.).

Sicily is more intensely infected than the mainland, both on the coast and in the interior, and especially the southern half of the island. Sardinia has also foci of the most virulent kind, and the same is true of the eastern coast of Corsica.

For the study of malaria in Italy we recommend the chart issued in the year 1894 by the "Direzione generale della statistica del regno." This shows in colors the malaria mortality for the three years 1890, 1891, and 1892. We draw from this splendidly executed chart that extensive foci (for instance, the Campagna) exist in Italy, in which the yearly malaria mortality amounts to 2 to 3 per cent. of the population. In a considerable number of places (the Pontine marshes, many places in Sardinia) the mortality exceeds 8 per cent.

The Pyrenæan peninsula shows foci on the south and west coasts (fewer on the east coast) and along the marshy banks of the Guadiana, Guadalquiver, Tajo, etc. We find the disease also on the plains of Castile and Estremadura (Madrid and Merida). Among the Balearic Islands Majorca is strongly infected.

In *France* the most malaria is found in the south and west. On the west coast it is especially the salt marshes (Marais salants) employed in the salt industry between the Loire and the Seudre that develop foci. Notorious is the vicinity of Rochefort, Marenne, and Brouage. Larger centers are found west of the Rhone delta. In the interior of France, Dombes, Sologne (Loire and Cher), and Brenne (Indre) are swampy and infected.

In *Switzerland*, in the southern portion of the Canton Tessin and surrounding the outlet of the Rhone into Lake Geneva, the disease is not uncommon.

Germany.—In the southwest, on the banks of the Rhine (in lower Alsace and in the Pfalz and Rhine valleys) and along the lowlands of the Danube, malaria is not infrequently found. It is almost never seen in central Germany, but appears occasionally in the North-

German lowlands (along the course of the Vistula, Oder, Elbe, Weser, and the Rhine), in Schleswig-Holstein, Hannover, Oldenburg, Westphalia, and in the low regions of the lower Rhine.

Among the European countries *Holland* was, in the past, the worst infected, and even yet shows the disease widely distributed, though decidedly decreased in severity. The low-lying districts of Belgium, especially the provinces of West Flanders and Antwerp, display numerous endemic foci.

Great Britain at the present day is entirely free from the disease.

In *Denmark* it is endemic on the islands Laaland and Falster.

Scandinavia.—Though Norway is almost exempt, Sweden has recently shown several endemic foci (Hedemora, Kalmar, Hudiksvall).

ETIOLOGY.

Our knowledge of the etiology of malaria has been enriched to such an extent in the last ten years that we may consider the disease among those the etiology of which is best known.

Among the etiologic factors there are three, the exposition of which is almost complete. The first relates to the telluric and climatic conditions necessary for the existence of malaria; the second, to the parasitology of the blood and internal organs; the third etiologic factor, its transmission by particular species of mosquitos, has been elucidated only within the last few years. This subject is discussed in an appendix to this article. (See p. 115.)

CLIMATIC AND TELLURIC REQUISITES.

The relations coming into consideration under this head are so manifest that they were partially recognized, even by the oldest observers. That the ancients came to speculative conclusions that have only recently been verified by the microscope is well known, and Terence is correct when he says, "Nihil dictum quod non dictum prius." Varro writes: "Advertendum etiam si qua erunt loca palustria, et propter easdem causas, et quod arescunt, crescunt animalia quædam minuta, quæ non possunt oculi consequi, et per aëra intus in corpora per os ac nares perveniunt, atque efficunt difficiles morbos." We have similar intimations from Columella, Palladius, Vitruvius. Richardus Morton expressed the same, many centuries afterward, only more precisely and correctly, when he wrote*: "Aer item externus, præsertim palustris vel autumnalis inspiratus, et cum spiritibus commixtus, particulis heterogeneis et venenatis ita nonnunquam refertus est, ut febres intermittentes non alia de causa in locis palustribus, et oris maritimis endemiæ fiant, atque, autumnali tempore, fere ubique epidemiceæ evadant." Soon after came Lancisius, with his investigation of the noxious emanations of swamps. His magnificent work is practically the first detailed attempt to determine the etiology of malaria. He speaks decidedly for the view that the injurious agents arise in swamps. He quotes, among others, a letter of the Würtemberg court physician, Rosinus Lentilius, on a severe epidemic of malaria in Stuttgart which ceased at once after a marsh situated in the city had been drained and laid out in gardens (Cap. iii).

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* "Pyretologia," Exercitat 1, Cap. iii.

In later times very many writers have associated the meteorologic and geologic conditions of malarial places with the development of the disease, and are almost unanimous in asserting an intimate connection between these conditions and the disease.

Among the climatic factors may be mentioned, first, warmth, moisture, and wind; among the telluric, the geologic formation of the soil, the amount of organic matter it contains, the conformation of the ground, and its elevation.

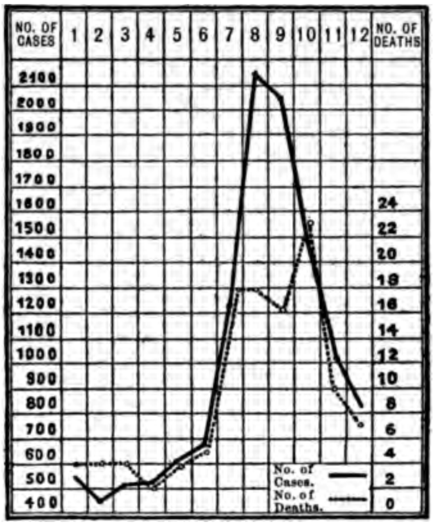

FIG. 1.—Morbidity and mortality of malaria in the French army in the year 1890 (after Laveran).

Heat.—The influence of heat on the origin of malaria is evident from the distribution of the disease on the earth's surface. Proceeding from the poles to the equator, the higher becomes the average temperature, and the more numerous and severe the foci of malaria. We have previously mentioned that, according to Hirsch, the isotherm between 15° and 16° C. marks the boundary for the occurrence of malaria; places, therefore, with a lower average summer temperature are spared the disease.

A second fact, indicating the important rôle of heat, lies in the distribution of malaria over the different seasons. Here we find that the acme of epidemicity always falls in the warm half of the year. This applies, with certain modifications, to all places. In the slightly infected malarial regions the maximum of cases occurs in spring and autumn, a remission is seen in summer, and the minimum occurs in winter. In warmer countries, as Italy, southern France, Greece, southern Hungary, Algeria, etc., as well as in tropical and subtropical countries, the maximum falls in the months of July, August, and September. (See Fig. 1.) Yet the less the variations in temperature and humidity, the more these relations are obliterated. Therefore we do not always see the sharp curves of Fig. 1, which illustrates the conditions in Algiers, because there are constant fluctuations of increase and decrease in the spread of an epidemic. In Sénégal the number of cases during and immediately after the rainy season (July to September) increases enormously. In Guiana and in the Antilles the distribution is, corresponding to the climate, more regular, yet even here most of the cases occur in the second half of the year, especially the third quarter, in conformity with the elevated temperature and increased rain.

The following statistics of admissions to the Hospital San Spirito, in Rome, of which the great majority are malarial patients, illustrates also what has been said:

MONTHS.	1864	1865	YEARS.			
			1873	1874	1877	1878
January	284	195	853	595	638	661
February	228	198	681	528	519	543
March	189	170	711	747	544	502
April	168	151	653	675	564	576
May	112	114	669	584	480	504
June	83	88	409	331	339	375
July	439	340	1130	865	1858	398
August	1492	570	2824	2647	2373	1604
September	1056	476	2185	2019	1995	1896
October	775	437	1761	1732	1460	1495
November	431	275	1280	1186	795	1245
December	271	205	777	773	695	1193
	5528	3219	13933	12682	12265	10992

It is important to realize that not merely the number of malarial cases, but also their severity, increases with a rise in the temperature. In temperate climates we find in spring the mild intermittent (viz., tertian); with July the severe forms begin to appear, and reach their acme in the months of August and September. The Italians, therefore, very practically classify them as vernal and estivoautumnal fevers. In winter the relapses occur. Many writers state that they have observed quartan fever principally in autumn and winter. It would be very interesting to discover if these were relapses from the spring or fresh cases. Four cases of pure quartan which I observed began as follows: September 26, the beginning of September, August 25, and the end of July. It seems to me, therefore, that quartan infection is to be collocated not with the spring, but with the late summer, fevers.

A complete picture of the distribution of malaria in the different seasons was drawn by Lancisi: "Itaque principio æstatis febres ut plurimum tertianæ non malignæ corripiunt: adaucto vero æstu, febres continuæ, atque etiam exitiales urgent; longe tamen deteriores evasuræ et plane pestilentes circa Æquinoctium autumnale, præcipue si pluviæ, nebulæ, rubigines, ventique australes accesserint. Tandem circa hyemale solstitium de pernicie ubique remittunt; sed in chronicas affectiones abeunt: qui enim ab ejusmodi Castrensibus febribus liberantur, fere semper contumacibus viscerum obstructionibus, et quartanis longo dein tempore duraturis divexari solent" (Cap. xi).

A further fact, showing the effect of heat, is that malarial epidemics occurring about disease foci are more severe in warm than in cool summers. Moreover, during especially hot summers malaria breaks out and becomes even epidemic over large stretches of land ordinarily not infected.

Yet with the recognition of the important effect of heat on the development of malaria it must be remembered that heat, of course, is only a factor which modifies the development of the parasite in the mosquito. That the influence of heat may be counteracted by other factors is shown by the previously mentioned circumstance that in mild malarial regions a decrease in the disease is observed during the warmest months, followed by a recrudescence in autumn. This striking fact loses somewhat in significance when we remember that malaria has an incubation period of two weeks and over. The cases, therefore, which break out in autumn must be referred back somewhat to their date of infection.

There remain to be explained the epidemics mentioned in the literature as occurring in winter. It must not be forgotten that in the discussion of the development of an endemic we take into consideration only new infections. In the case of relapses the climatic factors are not so important. According to the majority of investigators, the fevers occurring in winter are usually relapses from a summer infection, for it is the common experience that when the summer epidemic is wide-spread, the number of cases during the winter increases. Moreover, in this case cold may be of importance, inasmuch as many assert that "colds" are capable of bringing on relapses.

Moisture.—The humidity of the soil also participates in the development of malaria; the reason of this old-established belief is now clear to us. In the large majority of malarial foci yearly experience demonstrates that the severity of the epidemic is dependent on the amount of rain-fall—that is, the greater the amount of rain, the more prevalent is the disease. The following is the common observation:

When rain occurs during the warm season after a period of drought, there is an increase in the number of cases; but when the rain is continuous and floods the ground, the number visibly diminishes, only to rise after the rain has ceased and the sun has caused evaporation of the surface water and the formation of numerous small collections of water. This is evident, especially in the tropics; Fayrer, for instance, asserts that the greatest number of cases occur in India just after the rainy season, during the months from September to December.

The development of malaria is, therefore, favored by a certain degree of superficial water, but retarded if this is exceeded.

Consequently the severity of an epidemic is not absolutely dependent on the quantity of rain-fall, since lesser amounts at intervals between which the ground has an opportunity of drying are more favorable than weeks of continuous rain, especially when the temperature is low.

Jilek studied the connection between the amount of rain and the morbidity from malaria in Pola, and has given us the following statistics:

EPIDEMIC YEARS ARRANGED IN A DECREASING SCALE.	AMOUNT OF RAIN IN PARISIAN INCHES.	PERCENTAGE OF MALARIAL CASES.
1864	18.44	51.4
1863	14.25	48.6
1860	12.10	36.3
1865	3.44	35.4
1867	5.49	22.9
1868	1.50	14.2

The contradiction between 1865 and 1867 is explained by examination of the period during which the rain-fall took place.

The same is seen from the following table:

YEAR.	NUMBER OF MALARIAL CASES IN ROME TREATED IN THE HOSPITALS AND BY THE DISTRICT PHYSICIANS.	RAIN-FALL IN MARCH, APRIL, AND MAY IN MILLIMETERS.
1871	11.355	185.8
1872	19.232	251.3
1873	21.907	187.7
1874	20.286	225.8
1875	14.156	258.7
1876	17.588	205.0
1877	16.761	191.9
1878	18.875	101.8
1879	34.217	369.9
1880	22.699	209.8
1881	20.376	227.3
1882	19.704	115.7

An incontrovertible proof of the importance of moisture in relation to malaria is shown by the circumstance that the banks of still or running waters of every kind and marshy regions are the most frequent seats of the disease. The worst hotbeds in the world are on the banks of rivers, the coasts of seas, and in swamps. The floods occurring in spring pave the way for the estivoautumnal fever that thrives the more luxuriantly the more intense the subsequent heat. This flooding may be carried out artificially for industrial or agricultural purposes (rice-fields, fish-ponds, improvements, etc.), and produces the same effect as natural inundations.

Even very small water-basins, like puddles or circumscribed swamps, can give rise to localized malarial foci when the other requirements, which we now know to be infected mosquitos, are present.

That malaria can be intense in dry regions is equally certain, but we have a complete explanation in the fact that sources of water abound during the rains, to disappear completely in the dry weather. The anophelines bred earlier in the year still live and transmit infection through the period of drought.

It is probable that such an explanation is applicable to the statement of Vincent and Burot that, during the campaign in Boeni (Madagascar), malaria raged most frightfully from May to September, although the heat was moderate and not a drop of rain fell.

The relation of swamps, marshes, ponds, etc., to malaria has for a long time attracted the attention of observers. Malaria was even regarded by some as a disease occurring only in swampy regions, and this assumption was expressed in the names "swamp-fever" and "paludismus." It need scarcely be stated that this is a completely false idea. It is true now, as in the past, that marshy regions are usually infected with malaria, and that the worst foci are found in such places. Still there are swamps of large extent which show also the other requirements necessary for the origin of the disease that manifest no, or relatively little, malaria, while localities possessing nothing of a swampy character are sometimes hotbeds of the disease.

It may be laid down as a rule that swamps are more insalubrious the more level their surroundings; in other words, the more frequently a portion of the ground is laid free and flooded by alternating dryness and rain. Moreover, salt-water swamps along sea-coasts (brackish water) are usually particularly unhealthy.

The importance of swamps in the origin of malaria has been proved many times by the disappearance of the disease on draining them.

Still there are numerous examples of swamps which, on account of their situation in tropical and subtropical countries, seem especially adapted to breed malaria and yet are free from it; for instance, the swamps of New Caledonia, in which work may be undertaken without danger (here even the brackish water swamps are found free from the disease); the pampas of the Rio de la Plata, etc.

The reverse—namely, the occurrence of severe malaria in places having no swamp characteristics—may be found quite as frequently. In the first place, there is the Roman Campagna (Agra Romano), for the characteristics of which we must thank the searching investigations of Colin; again, the Punjab, where, according to Fayrer, the soil is dry, and water lies 50 to 100 feet below the surface; but where numerous sources of water occur, not to mention the irrigation canals, prolific sources of anophelines; finally, the dry, barren plateau of New Castile and the plains of Iran.

Ground.—Malaria is a disease the origin of which is associated with the soil, and the proposal has been made to designate it as a telluric disease.

It has been frequently confirmed that ships' crews are safe, so long as they remain on board (certain exceptions are mentioned below), even when the vessel lies near such an infected coast that a few hours' sojourn on land is sufficient to contract the disease. Vincent and Burot, for example, reported from the campaign in Madagascar (1895) that while the land troops were decimated by malaria, the marines and sailors on the ships, scarcely 300 meters from shore, remained unaffected throughout months.

The influence of the soil is further evidenced by the well-known fact that excavations in malarial districts are exceedingly dangerous, and that even in otherwise non-infected localities they are frequently followed by epidemics in the laborers or residents. The building of railroads, canals, fortifications, and streets, the cultivation of virgin soil, and the clearing of woods in malarial regions have cost innumerable human lives. These and other well-attested examples have now received their explanation from the occurrence of anopheles (infected) under such conditions.

Experience teaches that the soil is the more insalubrious the less it is cultivated. A striking example of this is the Roman Campagna. In ancient times this was well populated and cultivated, as is proved by numerous monuments and history, but with barbarian invasion and social decline the population disappeared and the ground was neglected.

In the cultivation of the soil we include several factors—namely, the regulation of the ground moisture by canalization, drainage, etc., the growing of plants, which, by using up the water, contributes to the drying of the soil, and finally the number of the population, etc.

The geologic characteristics of the soil come into consideration only in so far as they are connected with ground moisture and surface water—that is, the mineral composition is more or less irrelevant, while the porosity is important.

Malaria thrives least on a soil from which the moisture quickly runs or is quickly absorbed; best on a soil which retains its surface water in pools, etc., and only gradually gets rid of it by evaporation. Accordingly, barren rock soils, except where they retain water in hollows and pockets, and deep sandy soils are immune; but a basalt or granite soil covered by a layer of clay or other porous earth (even sand) is dangerous.

The *configuration of the ground* is important, since on it depends the regulation of the surface water. Ditches, troughs, and similar excavations which possess no outlet are, in connection with other conditions, very favorable to the disease; while a cone-shaped elevation from which the rain flows quickly is least favorable.

There are in the literature several instances of malaria among the crews of ships, the holds, storerooms, etc., of which were dirty or poorly ventilated, so that molds developed in the drains and elsewhere (Holden, Siciliano, and others). The principal thing to be said is that the clinical descriptions of these cases are by no means convincing that they were malaria and not other infectious diseases.

Van den Korput and Hammon were infected with malaria in a region free from disease through, so they think, having in their sleeping-room an aquarium for the breeding of certain algæ. Van den Korput further affirms that his instructor, Morren, in Liège, had warned him against keeping the aquarium in the sleeping-room, since he (Morren) had already observed that malaria developed at the time of the fructification of the spores. Similar assertions were made by Schürzf, Zwickau, and others. Unfortunately, we must say again the proofs are insufficient to establish the presence of malaria absolutely. In similar cases blood examinations would be of the greatest interest.

The *elevation of the ground* is of unmistakable influence, since with increasing height cases usually decrease in number and severity, though there are not a few highly situated infected places. This influence is probably exercised by the absence of the factors mentioned previously as the chief ones, namely, warmth and surface water, together with the requisite anophelines. Hirsch gives for the Alpine regions of Germany, 400 to 500 m. elevation as the boundary of malaria; in Italy it rises to 1000 m. On the slopes of the Himalayas, on the elevated plains of Ceylon, on the eastern inclination of the Rocky Mountains, the disease is found here and there at a height of 2000 m., and on the Peruvian Andes at even 2500 m. and over. These figures need no further explanation.

If the corresponding requirements are present, especially if a dry hill rises from a moist warm valley, the difference as regards local conditions of breeding-places of anophelines between two places lying close to each other may be striking.

Laveran mentions that the inhabitants of Constantine (Algeria), a city situated on rock ground 600 m. high, almost never suffer from malaria, while in the valley of the Rummel, about 130 m. lower, almost no one escapes. The same is true of Bona and numerous other places. It is consequently natural that in infected regions the more highly situated places should be chosen for settlement, and especially in summer should be made serve as resorts of refuge.

Moreover, height exercises an influence for other reasons, for experience teaches that the higher the elevation from a malarial soil, the less is the danger of infection—*i. e.*, from the bite of anophelines.

From innumerable observations it appears that the "malarial virus" can rise only an inconsiderable distance above the ground, so that residence at a certain elevation above the insalubrious soil diminishes the danger of infection. This knowledge has been put into practice, in that laborers working in malarial regions build their huts on piles several meters high in order to be out of danger during the night.

From what has been said it is evident that certain factors, like warmth, moisture, and soil, may be necessary to the development of malaria, yet these factors are by no means sufficient to produce the disease. They are simply factors which influence, in one way or another, anophelines and the parasites which they convey. It is thus clear that two places may exist under exactly similar telluric and climatic conditions, yet one be healthy, and the other severely infected. In the former case all the external requirements for the development of the parasite are present except the anopheline, indispensable for its transmission. Again a region may seem unsuspicious on account of its telluric and climatic conditions, and still be infected, owing to the presence of anophelines (and cases of malaria, active or latent).

In this way only can we explain the malarial epidemics that occasionally spread over districts at other times immune, and the becoming healthy of insalubrious districts.

THE MALARIAL PARASITES.*

The suspicion that malaria was caused by a living contagium has been entertained from the most ancient times and repeatedly expressed by even the oldest writers (Vitruvius, Varro, Columella).

Lancisi considered the emanations of swamps to be carriers of small animal organisms and eggs, which gained entrance to the body by way of the respiratory or digestive tract. Lancisi pictured to himself an infection of the body by small worms, and advised the examination of the fresh blood, though he confesses that he himself, neither in abscesses (spontaneous nor artificially produced) nor in the gastro-intestinal tract of fatal fever cases found worms that were out of the common.

During the decline of the last century, to which medical science owes so much, the question of the parasitic etiology was vigorously pushed and finally successfully proved. Rasorr declared for the parasitic theory in 1842; Mitchell, in 1849. These declarations were followed by numerous painstaking investigations of the air, the water, and the soil of malarial regions, and of the secretions and excretions of patients, with the result that a series of vegetable and animal organisms were brought forward as excitants of the disease. The names of these pioneers will always hold an honorable place in the history of medicine, even though their efforts were in vain: "In magnis et voluisse sat." We may name Hammond, Lemaire, Salisbury, Eklund, Klebs, Tommasi-Crudeli. Still we will refrain from discussing their discoveries and theories, since the investigation of the last eighteen years has shown that their findings were delusions and that the true discovery belongs to a more fortunate master. This is A. Laveran.

The discovery of the malarial parasites by Laveran took place on November 6, 1880. This investigator found himself, at the time, in service in Constantine, a markedly infected malarial station in Algeria, and, taking advantage of the favorable opportunity, he endeavored to revise anew the pathologic anatomy of the disease. He began the study by investigating the formation of the pigment in the organism.

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* We introduce here only what is of importance to the clinician, and for further study must refer to the special works of Laveran, "Du paludisme et de son hematozoaire," Paris, Masson, 1891; Marchiafava and Bignami, "Sulle febbri estivo autunnali," Rome, Loescher, 1892; Mannaberg, "Die Malariaparasiten," Vienna, Hölder, 1893; Thayer and Hewetson, "The Malarial Fevers of Baltimore," Baltimore, the Johns Hopkins Press, 1895.

A logical, as well as fortunate, idea induced him to study the pigment in the blood of the living patient in order to complete the findings in the vascular system of the cadaver. Although previous to this time many other investigators had studied microscopically the blood of malarial patients and recognized therein certain pigment-containing bodies which could be differentiated from the pigment-carrying leukocytes, Laveran was the first to conjecture the parasitic nature of these bodies and convince himself of it by a long investigation. This new explanation of previously recognized pictures, passed over without presentiment by numerous observers since Heinrich Meckel, is the more creditable to Laveran since his discovery occurred at a time when the Klebs-Tommasi-Crudeli Bacillus malariæ (confirmed, as it was, by many) seemed to have determined the etiology of the disease. Laveran found his conjecture, that the hyaline pigmented corpuscles were parasites, confirmed when he observed, on November 6, 1880, several long flagella escape from such a corpuscle and pass across the specimen with lively, whip-like movements. On account of their flagellar shape, he considered that they belonged to the genus *Oscillaria,* and proposed for them the name of Oscillaria malariæ. It was only later that these motile bodies were properly classified with the protozoa, among the lowest animals. Laveran's discovery was at first confirmed only by his colleague, Richard.

The bodies which Laveran claimed to be parasites were for years described by other writers as phenomena of degeneration in the red blood-corpuscles, and this opinion was even until very recently held by isolated individuals.

The general recognition of Laveran's discovery may be dated from 1885, when his investigations were confirmed by Italian observers, especially Marchiafava and Celli. In addition to these two names, we must not omit that of Golgi, who determined the connection between the fever symptoms and the different stages of development of the hematozoa, on the one hand, and between the fever types and forms of parasites, on the other. It was owing to his clever comprehension that the numerous forms brought to light by other observers without attention to their biologic and clinical significance were separated and placed in their natural relations. Following the methods which he applied to the quartan and tertian fevers, Marchiafava and

Celli, Canalis, Bignami, and others have endeavored to put under the same rules the pernicious summer and autumn types.

Golgi's investigation, moreover, brought up the question of the unity or multiplicity of the malaria micro-organism, one of the most interesting and important since Laveran's discovery, though thus far there is little unanimity of view in regard to it.

At the same time attention was directed by Celli and Guarnieri, Grassi and Feletti, the author, Romanowsky, Sakharoff, Ziemann, and others, to a second very important consideration, namely, the structure of the parasites. Omitting details, this question is practically settled.

A further problem arose in relation to how quinin acted, in consideration of the new teaching. The majority of the investigators already mentioned took this up, and it, too, seems to be satisfactorily determined.

Recently the greatest interest has centered in the question of the existence of the parasites in the external world, and their mode of entrance into the human organism. How, too, this problem has been solved, we will see later.

By a fortunate coincidence, shortly after Laveran's discovery, Gaule found in frog's blood, Danilewsky in the blood of lizards, turtles, and certain birds, hemoparasites that, morphologically, showed a striking similarity to the malarial parasites of man.

Methods of Examination.—The examination of the natural (unstained) blood is of greatest importance to the clinician, though the making and examination of dry preparations are also very valuable, especially when the microscope is not at hand at the bedside.

The examination of unstained preparations is made as follows: A very thin cover-glass and a slide are cleansed with water and alcohol and thoroughly dried. The tip of the finger or lobe of the ear is washed with soap and water, dried, and pricked with a needle or lancet. The first drop is wiped away with a linen cloth, and a second very small drop allowed to issue forth. The summit of this drop is touched with the middle of the cover-glass held in forceps, and the cover-glass is at once laid on the slide, where the blood-drop quickly spreads out between the two. It is not advisable to assist the spreading by pressure, since the mechanical injury may bring about changes in the shape of the corpuscles. The best results are obtained with the thinnest cover-glasses; in fact, with thick ones labor is in vain. If, as is usual, several preparations are made one after another, the drop of blood remaining must be wiped away each time and a fresh one pressed out for every new preparation. The proper size of the drop is learned by experience, though it may be said that tyros in blood examinations always employ too large drops. The preparation is successful only when the red blood-corpuscles are isolated one from the other and present to the observer their flat surface unaltered. Rouleau-formation, thornapple appearance, etc., make this examination more difficult or even impossible.

For the microscopic examination a good immersion-lens is useful; in fact, indispensable if the details of the hematozoa are to be studied, though it is possible, with a good dry system (400 to 500 diameters), to see the different forms, especially if the observer has a certain amount of experience. It is well known that Laveran made his discovery with a low power and found even the smallest forms.

The complete study of the preparation may require considerable time. In severe cases it is not rare to see a number of parasites in every field when the examination is at once successful, but in mild cases, and occasionally in pretty severe ones, an entire preparation may be gone over before a parasite is encountered. For these cases a movable stage is very convenient. The time in the course of the fever at which the examination is undertaken plays an important rôle, since the parasites are usually found most numerous in the peripheral blood from several hours before the paroxysm to its acme, though they may be absent. On the other hand, when the temperature has again fallen is an equally good time to make the examination.

Dry Preparations.—If there is no microscope at hand to examine immediately the natural blood, or if there is any other reason for making the examination later, dry preparations are made and studied after staining.

These dry preparations are made in two ways—either by placing on the cover-glass containing the drop of blood a second cover-glass, allowing the blood to spread out between them, and sliding them apart, or by drawing the edge of a cover-glass through the drop on the finger-tip and drawing this, inclined at an angle, over a second and a third. Equally good preparations are obtained by spreading the blood on a slide with the shaft of a straight needle. The drops must naturally be small, for the layer of blood should be so thin that the individual corpuscles are isolated from one another and present their flat surface to the observer. The cover-glasses or slides are dried as rapidly as possible by waving to and fro. After they are thoroughly dried, the preparations are fixed in equal parts of alcohol and ether or simply absolute alcohol for five minutes. Their further manipulation is dependent on the stain to be used.

Staining.—For clinical purposes the best stain is the Romanowsky-Ziemann stain or any of its modifications. [It is made in the following way:

Solution A:

Medicinal methylene-blue	1.0 part
Sodium carbonate	0.5 "
Water	100.0 parts

Keep in an incubator or in the sun until the solution, originally blue, becomes a deep purple. This change takes place in a few days.

Solution B:

Eosin A G brand or B A brand or pure eosin for blood work	1 part
Water	1000 parts

For staining, dilute each of these solutions 20 times with water. Mix equal parts of each solution and pour on the slide. Stain for five to twenty minutes. The nuclei of the leukocytes, the platelets, and the nuclei of the parasites are stained a deep "red." This stain is readily made, never fails, and makes the detection of parasites an easy matter. It, moreover, gives characteristic staining effects, "stippling" of the red cell in the case of the simple tertian parasites, and also, though under what exact conditions is not certainly known, in the case of the malignant tertian parasite, though the stippling is in this case of a different character. A variety of other stains, but none so satisfactory as this, may be used, such as Löffler's alkaline methylene-blue and methylene-blue and eosin.—Ed.]

In using Löffler's methylene-blue (30 c.c. of a concentrated alcoholic methylene-blue solution + 100 c.c. of a 1 : 10,000 caustic potash solution) the preparation is, after fixation in alcohol and ether, dried between filter-papers, placed for about a minute in the staining solution, washed in water, dried and mounted in xylol Canada-balsam. The red blood-corpuscles remain unstained. The parasites and the nuclei of the leukocytes (and the nuclei of erythroblasts, if there are any) are stained blue.

In the second case the preparations are placed on a half-concentrated watery methylene-blue solution* for half an hour, washed in

* It is best to have ready at hand a concentrated alcoholic solution of methylene-blue, from which the watery solution is prepared fresh when desired. This is readily done by mixing about five drops of the alcoholic mother-solution in a watch-glass of water.

water, dried with filter-paper, and counterstained with a 2 per cent. eosin solution in 60 per cent. alcohol for five minutes, washed in water, thoroughly dried, and mounted in xylol Canada-balsam. The leukocytes and malarial parasites are stained blue, the red blood-corpuscles and the eosinophile granulations, red.

Instead of methylene-blue, hematoxylin may be used.

Thionin has been highly recommended by Marchoux. It is employed in the following solution: Concentrated alcoholic thionin solution (alcohol 60 per cent.), 20 c.c.; 2 per cent. watery carbolic acid solution, 100 c.c.

The mixture may be used after fifteen days. It stains in a few seconds. The leukocytes and parasites are stained red violet.

For the staining of hematozoa in tissues Bignami proposes the following: Fix very small cut pieces in 1 per cent. watery solution of bichlorid of mercury to which has been added 0.75 per cent. NaCl and 0.5 per cent. to 1 per cent. acetic acid. The sections should remain in this from one-half hour to several hours. They are then transferred to alcohol containing a little iodin (sherry color), and finally hardened in alcohol.

The staining is effected in a saturated watery or alcoholic solution of safranin, methylene-blue, vesuvin, or magenta red. The preparation should remain for five minutes, and is then washed in water.

Under special circumstances it may become necessary, for the purpose of diagnosis, to examine the blood of the internal organs. This occurs in cases in which there is strong suspicion of malarial infection, though the examination of the peripheral blood is negative. There are, for instance, rare cases of very severe malarial infection in which the capillaries of certain organs, especially the spleen, liver, and brain, are filled with parasites, while the peripheral vessels show only a few infected red blood-corpuscles. In order to assure the diagnosis in such a case puncture of the spleen is indicated. Though, as a rūle, this operation is without injurious results, it is not to be undertaken without sufficient reason. We must consider as a decided contraindication to puncture of the spleen any disease in which there is an inclination to hemorrhage, since profuse, even fatal, hemorrhages might result from the wound.

The puncture is to be done by a Pravaz syringe under strict aseptic precautions. During the operation the patient should be told to hold his breath, so that the wound is not enlarged by the upward and downward movement of the spleen in respiration. After the operation an ice-bag is applied to the site in order to relieve any pain and produce contraction of the spleen, so as to prevent hemorrhage.

[For diagnosis the practitioner should adopt the Romanowsky method, but examination of unstained fresh preparations should not be neglected, though to the beginner the pitfalls in an unstained specimen are many.—ED.]

GENERAL AND SPECIAL MORPHOLOGY AND BIOLOGY OF THE MALARIAL PARASITES.

The malarial parasites are unicellular organisms whose cycle of development from beginning to end takes place within the red blood-corpuscles. They are, therefore, parasites (cytozoa) of the erythrocytes, and on this account occupy a special position in pathology.

The young forms show a more or less ameboid movement, while the adult organisms change their form but little, and then not so much by the protrusion and drawing-in of pseudopodia as by the contraction of certain layers, which results in a very gradual change of shape.

On account of the alterations in form produced by the ameboid movement we can describe no typical shape for the young parasites. As a matter of fact, they change constantly under the eye of the observer. Only after exposure to external influences and their consequent death do we see anything like a constant form. This is usually that of a ring, occasionally a disk.

Their growth within the flat red blood-corpuscle makes it easy to understand why the young and half-grown parasites show usually a flat disk form; otherwise the parasite appears, depending on whether it is at rest or in ameboid movement, round, oval, or with regular or irregular contour. The adult parasite, especially when it has escaped from the red corpuscle, is usually spheric, yet there are stages in its development that show more or less constant crescent, spindle, and oval forms. The parasite measures, according to its age, 1 to 10 μ.

The parasites usually occur isolated in single blood-corpuscles, yet it frequently happens in the case of certain varieties that several (two to six and over) are found in the same corpuscle.

The body of the parasite is colorless, and in the living condition shows no structure, appearing as a homogeneous, hyaline mass. A nucleus or granulations are only occasionally observed, and then only in particular varieties (for instance, the quartan parasite) or in full-grown forms.

The young parasite appears like a small speck in the red blood-corpuscle, and depending on whether the parasite is deep in the corpuscle or near its surface, the speck stands out more or less clearly. It is diagnosed by its frequent change of shape, the result of its ameboid movement; though it must not be forgotten that this movement may cease temporarily or even entirely. On a warm stage it is more lively than on a cold one.

At this time, before the pigment-granules appear, the parasite is very difficult to see and to recognize. Still in severe malarial regions a close acquaintance with these small, non-pigmented or very slightly pigmented organisms is very important, since the parasites of estivoautumnal fever occur in the peripheral blood only in this stage, and later, when they develop pigment, they are found almost exclusively in the capillaries of the internal organs. Parasites of the quartan variety are, even in the second half of their existence, usually found in the peripheral blood.

In addition to an increase in size and a gradual slowing of movement the quartan parasites are characterized by their pigmentation.

This pigment (malarial pigment, melanin) is nothing else than the product of digestion of the hemoglobin, at the expense of which the parasite is nourished. It appears in the form of very fine, dust-like particles, in the form of larger granules, lines, needles, grains, or clumps. The longest needles or lines measure about 1 μ. By the running together of numerous pigment-granules larger clumps, in the shape of glandular masses, are formed. The color of the pigment is, in the last-mentioned rough masses, black, while the fine needles, granules, and dust are usually reddish brown. Laveran described the color as a dark, fiery red ("rouge feu trés foncé"). Very rarely the pigment is light blue or greenish.

Concentrated mineral acids have no effect on the pigment, but it is cleared by weak alkalis, after the action of which it appears reddish brown or yellowish. The pigment is dissolved by ammonium sulphid (Kiener). The Berlin-blue reaction cannot be obtained from the pigment.

According to Kelsch and Kiener, melanin shows a similarity in its microchemic behavior only with the pigment of melanotic tumors. It is entirely different from the iron-containing or iron-free transformation products of hemoglobin found in hemorrhagic foci. The amount and appearance of this pigment vary in the different varieties of parasites, but about this we shall speak later on.

The pigment-granules participate in the ameboid movements of the parasites in that they move in and out with the pseudopodia. Yet in addition the pigment shows a second communicated movement, which is most marked in the adult sexual forms of the parasites. This consists in a more or less lively, to-and-fro wavering of the pigment elements. When slight, the pigment-granules move sluggishly, scarcely changing their place, but when marked, they whirl back and forth like a swarm of gnats. Laveran has appropriately compared the appearance in this last case with the bubbling of boiling water.

In my opinion this movement of the pigment is produced by the to-and-fro motion of the plasma, which, confined or relaxed by different circumstances, forces the pigment-granules more or less rapidly back and forth.

The duration of this motion varies, although in every case it continues much longer than any of the other movements of the parasite. I have observed it in the moist oxygen chamber for from twenty-four to forty-eight hours. According to Ziemann, it continues in the parasites in the cadaver.

Besides the pigment, we may sometimes find in the parasites small granules of undigested hemoglobin, recognizable by its color; again, non-contractile vacuoles, occasionally in large numbers, particularly in adult forms.

The last stage in the development of the parasite is that of multiplication. This is ushered in, as a rule, by the pigment which was previously irregularly distributed, concentrating itself centrally or eccentrically. Though this is the rule, it must not be forgotten that exceptions are very numerous, and that multiplication may take place while the pigment is scattered.

The principal feature in multiplication consists in the breaking-up of the mother-parasite into a number of small bodies, every one of which is complete in structure and possesses the power of independent existence. We designate these new organisms as spores, and their process of origin as sporulation.

Arrived at a certain stage of development, the parasite, therefore, sporulates. With this its existence ceases, and in its place several young organisms appear and continue its parasitic activity.

Besides these newly formed spores there remains a remnant of the mother-parasite, consisting principally of pigment. These pigment-rests are inanimate and are quickly taken up by leukocytes and vascular endothelium and so removed from the circulation.

At the time of their formation the spores lie within the mother-parasite, which, on its part, is within the remaining shell of the infected red blood-corpuscle. Rupture of this double shell is, therefore, necessary before the spores are free. This rupture may be observed not infrequently under the microscope.

The size and number as well as the other characteristics of the spores differ with the different varieties of parasites, but we will return to this when treating of the special peculiarities of the organisms.

In addition to sporulation, there is another very remarkable metamorphosis in the mature parasite, which, differing from sporulation, does not take place within the blood-vessels, but only after the blood has been exposed to external influences. It is observed when the microscopic preparation is studied some time (ten to twenty minutes) after the removal of the blood. This process consists in the sending-out of flagella.

These flagella are developed from large sexual (male) forms of the parasites. This highly interesting process is best studied in the spheric bodies of the crescent group (see below), and occurs as follows: The round parasite, which up to this time has lain immovable, except for the lively to-and-fro motion of the pigment within it, begins suddenly to show marked movements of contraction, associated with drawing-in and bulging-out of its margin. Soon after, glove-finger-like pseudopodia protrude from different places on the surface. These are limited by the membrane of the organism. This membrane resists the outward pressure of the flagella for some time (often entirely), yet eventually they break through, and while the plump pseudopodia sink back, their long, thin flagella shoot out and whirl around so rapidly that their contour is visible only now and then. The violence with which the flagella strike the red blood-corpuscles lying about, causing deep furrows in their substance (though these furrows quickly disappear), has been frequently described.

Small nodules which seem to change their place are often found on the flagella, and their free end is usually knobbed. Here and there fine pigment-granules are seen within them.

The number and arrangement of the flagella vary. From one to five may be observed on one organism, though they are often difficult to count on account of their rapid vibration.

Their movement continues about fifteen to thirty minutes, becoming gradually weaker, more intermittent, and finally ceasing. The motionless flagella may then be seen attached to the organism.

Frequently the flagella become separated from the organism and swim about in the plasma with a liveliness resembling that of an eel. These free flagella constitute the only form of malarial parasites which have to any degree the power of changing their location.

What is the signification of these flagella? Since he first observed them, Laveran has claimed that they represent the highest stage of development of the parasite, because they develop in the cell-body and escape at the time of maturity. They may be considered, therefore, as significant of the multiplication of the parasite. Up to the time when Laveran stated this he had not recognized the sporulation of the organism.

But little attention was bestowed by the Italian investigators on the flagella. Their occurrence was represented as exceptional, and the whole phenomenon of their origin was described by Grassi and Feletti as an agonic symptom of the parasite. This view was adopted at the time by many Italians, but in the light of recent discoveries has been universally abandoned.

In the course of my investigations I paid especial attention to the flagella, and came to the following conclusions: Flagella occur in connection with all varieties of malarial parasites. They are most frequently observed on the spheres that belong to the crescent group, almost as frequently on the tertian parasites, and more seldom on the quartan ones. From their frequency (which can be confirmed only by repeated and careful examinations of the blood) I concluded that the flagella are to be regarded as necessary attributes of the parasite in a certain stage of its existence.

In connection with some varieties of parasites, as, for instance, the common tertian, flagella may be found regularly, and often in large numbers, a few moments after the removal of the blood; a longer time—about ten to thirty minutes—is necessary before they appear on the crescents. I have been able to find flagella in most cases of malaria that showed numerous parasites, especially when the duration of the disease permitted several examinations.

In my opinion these forms were by no means the products of the agonic period, for in this case it would be inconceivable why so relatively small a number should occur at a time when all the organisms in the preparation are in the act of dying, and why they are not seen, at least here and there, in the circulating blood at the time of the paroxysm, or after the administration of quinin, when so many organisms are succumbing. Finally, the extraordinary activity of the flagella could scarcely be said to indicate that they are an expression of death.

Since 1893 my opinion has been that the flagella were organisms which act as intermediaries in the transition of the parasites to saprophytic conditions. I believed that the flagella represented the beginning of a life outside the human body, and that, as a result of the nutritive medium being unsuitable, these young saprophytes died.

My opinion was adopted by Manson, and developed further. He made the flagella flagellate spores ready to force their way into some cell not yet known outside the human organism, where they probably carry out the second half of their existence. The investigations of Sakharoff, according to which the flagella contain a chromatin substance, supported Manson's view.

In this regard Maccallum's discovery was of considerable value. He observed in the hematozoa of crows that the flagella bored their way into certain granulated parasites, which thereupon swelled up and moved away. He saw, though only once, the same occurrence in connection with the malarial parasites of man. Maccallum considered this to be a sexual act.

[The way in which Ross solved the problem of the nature of the flagella and gave proof that the bodies were male elements, whose function was to fertilize female cells, a process naturally occurring in the mosquito's stomach, is considered in the supplement to this article (see p. 115).—Ed.]

We have now to consider a form of malarial parasites which differs in shape from the varieties so far mentioned, and is characterized by this difference. This is the crescent and the bodies allied to it, namely, the spindles and spheres. We classify all these forms under the one head—crescents.

The typical half-moon bodies show a shape which is described in the name given them by Laveran ("corps en croissant"). They are slender, very delicate looking, strongly refractive, sometimes glistening bodies, about 8 to 10 μ long (seldom 20 μ), and 2 or 3 μ broad at the middle. They also contain pigment, though in varying amounts from a few isolated granules to large masses. This pigment is found either scattered irregularly in the organism or collected at one point, usually the center, where it is more or less thickly grouped. I have found this grouping very frequently in the form of an 8, and the final arrangement in two clumps or rows. Moreover, Babes and Gheorgiu have also observed and described this double division of the pigment.

When concentrated, the pigment is motionless; when scattered, it shows a slight trembling movement, which may be associated with a slight change of place.

The crescents possess no ameboid motion, yet show the power of gradually changing their shape.

Laveran has observed under the microscope half-moons develop to spindles, ovals, and finally spheres. This change of shape is scarcely perceptible, and often requires an observation lasting several hours to see it, yet sometimes it occurs in a few minutes.

While some crescents stretch out to a spindle or cigar shape, and by the gradual equalization of their diameters become oval or spheric, others may form at the bend a sharp angle which likewise modifies considerably the half-moon.

The transition of the half-moon into the sphere is followed by further changes. The pigment, up to this time immotile, and forming usually a pretty regular circle within the organism, begins to show the trembling and swaying movements mentioned above. After a short while the circle is broken up and the now scattered granules tumble actively about. The protrusion of flagella soon follows.

What is the relation of the half-moons to the red blood-corpuscles?

Laveran considered the crescents to be free bodies swimming in the plasma, and reported in his first communication that only here and there were they to be seen attached to red blood-corpuscles, from which they again separated themselves. Yet it must be added that Laveran, even in his first publication, described a fine line which, running in an arch, bound the two sides of the bow together. This fine line is nothing else than the boundary-line of the red blood-corpuscle, in the interior of which, as Marchiafava and Celli first recognized, the crescent develops. The blood-corpuscle is, therefore, as a rule, so decolorized that its substance is scarcely perceptible, and its presence is indicated only by its refractive margin, though sometimes we see a remnant of the hemoglobin still covering the half-moon. A blood-corpuscle usually contains only one half-moon, very rarely more than one.

The crescents, together with the spheres and ovals derived from them, are characterized by an especially sharp contour, so that the spheric bodies of the crescentic class are easily differentiated by the experienced from the spheres which constitute the adult parasites of the first group. In some instances we see a double contour, indicating that the organism possesses a membrane.

We may mention here some of the older views held as to the nature of crescents, though these have now only a historic interest.

Laveran considered the crescents and their spheres to be encysted bodies, in which, eventually, the flagella, regarded by him as a very important stage in the development of the parasite, would be formed. Councilman concluded, on account of their resistance to quinin, that they were spores. Antolisei refused to accept Councilman's view, because they contained pigment, and he looked on crescents as adult forms whose fate it was to die. Bignami and Bastianelli adopted Antolisei's opinion, and described them as sterile modified products of the ameboid parasites. Canalis believed that he observed sporulation in the crescent, but this was not confirmed.

While the writers so far unanimously agreed that crescents originated from small ameboid parasites that were capable of breaking up into spores, Grassi and Feletti denied this and claimed that they developed from ameboid parasites which were incapable of sporulation, and capable only of forming crescents. They consider these parasites as a particular class, and name them Laverania malariæ.

I proposed an explanation of the origin and significance of the crescent different from all others. I considered the crescents to be syzygies of the parasites of the second group. By syzygies zoölogists understand forms which develop from the copulation of several individuals—a kind of sexual hybrid; this is a phenomenon known to occur among different sarcodinia, sporozoa, and flagellates. Moreover, in certain blood gregarines of the frog and the lizard, which are nearly related to malarial parasites, these unions (congregations) have been seen; so, too, in Drepanidium princeps and Karyolysus lacertarum (Labbé).

The fact is that in cases of infection with parasites of the second group blood-corpuscles are frequently found containing two or more parasites; and I have several times directly observed the phenomenon of two such approximated parasites blending (melting) together.

For the grounds on which I based my conclusion that the crescents are syzygies of the ameboid parasites I refer the reader to my monograph on malarial parasites. I present here only those points which are explained by no other interpretation of the origin of the crescent. These pertain to the late period at which the crescents appear in the blood, the relatively small number of them in comparison with that of the ameboid parasites, and the obstinacy with which they remain in the blood and resist quinin. All these uncommonly striking circumstances are explained easily by the theory that the half-moons are syzygies.

My view was adopted by Manson, who regarded as organisms of copulation not only the crescents, but all parasitic forms that show the power of producing flagella.

Other writers, as Bastianelli and Bignami, Thayer and Hewetson, Ziemann, have failed to find in the blood the morphologic criteria on which I have based my view. One of these, namely, the arrangement of the pigment in figure-of-eight forms, is so frequent that it is unintelligible to me how it can be overlooked. Other more convincing phenomena, like the proof of copulation in natural and stained preparations, require, to say the least, very painstaking investigations. I see as yet no reason to deviate in the slightest from the standpoint taken by me in my earlier communications. The negative findings of the opposition cannot contradict what I positively and with all certainty observed.

Finally, we must especially insist on the extraordinary vitality of the crescents, in which they differ decidedly from every other form of the different parasites. Days, weeks, and months they may be seen in the blood, though the patient may be taking the largest amounts of quinin.

The relations of the malarial parasites to the red blood-corpuscles are evident from the following: The newly formed young parasites (so-called spores) remain only a short time in the plasma before they attach themselves to a red blood-corpuscle. They remain attached to the surface of the corpuscle but a short time, and then force their way into its substance, where they complete their development. This does not always terminate in multiplication; since, for unknown reasons, sporulation sometimes fails to occur. In these cases, after the parasites have reached a certain size, they break through the remnant of the corpuscle surrounding them and are found free in the plasma, where they often break up into several pieces of different sizes. All these organisms are to be looked on as degenerated parasites in which no further development occurs. Excepting the short period between the throwing-off of the spore and its entrance into a corpuscle, all the stages of development take place within the red blood-corpuscle.

Under the influence of the parasite, the red blood-corpuscles undergo manifold metamorphoses. In the case of the pigment-producing parasites, the blood-corpuscles are often more or less quickly decolorized, so that their remains are sometimes scarcely visible. Moreover, changes in size and shape of the red blood-corpuscles are frequently observed. In tertian fever the infected corpuscles are often hypertrophied even as much as twice to four times the normal size, and at the same time decolorized. On the other hand, diminution in size of the infected corpuscle is also observed, as in the case of the "globuli rossi ottonati," first described by Marchiafava and Celli. It is these shrunken red blood-corpuscles that show the color of old brass. They occur in cases of infection with the faintly pigmented parasites of the second group. For the sake of brevity, we describe them as "brassy corpuscles" (Messingkörperchen). The markedly pigmented small parasite lies sometimes in what appears like a rumpled white veil, consisting of the shrunken, completely decolorized corpuscle.

The corpuscles infected by the quartan parasites are often somewhat diminished in size, more deeply colored, but without other signs of shrinking.

It is not our purpose to go into details concerning the structure of the parasites, yet we may say that they show plasma, a nucleus, and a nucleolus. (See Plates VI and VII.)

Danilewsky observed, in two cases of chronic malaria, bodies within leukocytes, which he designated as pseudocysts and leukocytozoa. Nothing at present can be said in regard to their relation to the malarial parasites or to malaria in general.

THE UNITY OR MULTIPLICITY OF THE PARASITES, SPECIES OF PARASITES, AND TYPES OF FEVER.

Soon after Laveran's discovery the question arose whether there was only one parasite for all cases or whether different species were to be differentiated?

It seems to me that we may consider this question answered, even though a considerable number of observers, with Laveran at their head, still hold to the unity of the parasites.

Referring to my monograph for more minute details in regard to the arguments on both sides of the question, we will content ourselves here with only those points which determine us in defending the multiplicity of the malarial parasites. These are:

1. The morphologic differences of the parasites occurring in the different types of fever. 2. The results of inoculation, which show, with the exception of a few experiments that are not above criticism, a similarity of parasite and type of fever in the source from which the inoculable blood was taken and the person inoculated. 3. The unchangeableness of the parasites in any single case, provided no new infection takes place. 4. The differences in the parasites and the types of fever according to the season and the geographic location.

1. The morphologic differences between the parasites in malarial fevers of different types were first demonstrated by Golgi. For the

further development of this subject we have to thank the investigation of Marchiafava, Celli, Canalis, and Bignami. A detailed description of the peculiarities of the different species will be given later.

2. We refer to Table I, which shows 35 experimental blood inoculations. Of these, the first two of Gerhardt's are not fully available for our purpose, since no attention was bestowed on the parasites; yet even here it is to be remarked that the same type of fever occurred in the inoculated as existed in the person from whom the blood was taken. Of the other 33 experiments, in 31, the parasites found in the person inoculated were proved completely identical with those in the source. In only two cases (Nos. 3 and 4) was the result different. In these the blood of the person inoculated showed parasites of the second group, while in the person from whom the blood was taken only quartan parasites were discovered. Yet we have in another place shown, and the investigators in question have confessed, that both these experiments are not above criticism, and cannot, therefore, be considered as very convincing.

In all other instances the result supports the assumption that the different forms of parasites are to be regarded as species which are unchangeable and cannot be transformed one into another.

Moreover, if we compare the types of fever occurring in the person from whom the blood was taken and in the person inoculated, we find, omitting the two questionable experiments, Nos. 3 and 4, that that type of fever was always obtained which was to be expected from the species of parasite injected.

In 22 cases the type of fever in the person inoculated was identical with that in the source; in four experiments (Nos. 17, 19, 20, and 22) a new type was found in the person inoculated. Yet we can readily show that there is here only an apparent contradiction, for all these cases showed tertian parasites and a change between tertian and quotidian fever. It is now generally recognized that tertian parasites have a great inclination to cause quotidian fever, by a doubling of the generation (as a matter of fact, a double tertian). Accordingly, we frequently see in patients with ordinary tertian alternations between these two types. This has even taken place in cases produced experimentally. In cases No. 32 to 35 the type did not reach full development in the person inoculated, since the fever was at once treated with quinin.

Inoculation experiments show, therefore, that the types of fever go over into one another, even as little as the species of parasites, and that a change of fever type takes place only within definite limits, which are measured by the biologic relations of the parasite.

TABLE I.—EXPERIMENTAL INOCULATION OF MALARIA.

No.	OBSERVERS.	FORM OF PARASITE AND TYPE OF FEVER IN THE SOURCE.	INCUBATION.	FORM OF PARASITE IN THE PERSON INOCULATED.	TYPES OF FEVER IN THE PERSON INOCULATED.	AMOUNT OF BLOOD INJECTED. REMARKS.
1	Gerhardt.	Quotidian (parasite unknown).	7 days.	—	First irregular, then quotidian.	1 c.c.
2	The same.	Quotidian (parasite unknown).	12 "	—	Quotidian.	
3	Gualdi and Antolisei.	Quartan.	10 "	Organisms small, unpigmented, ameboid, later also crescentic.	Intermittent, irregular, sometimes subcontinuous, sometimes quotidian.	3 c.c. intravenously.
4	The same.	"	12 "	Unpigmented ameboid organisms or very slightly pigmented.	Mild, irregular.	3 c.c. intravenously.
5	The same.	"	15 "	(?)	Quartan.	3 c.c. intravenously; in the blood numerous sporulation forms.
6	The same.	"	12 "	Forms of the source.	"	
7	Antolisei and Angelini.	Tertiana anteponens.	11 "	" " "	Tertiana anteponens, then quotidian.	(?); intravenously. Blood taken at the beginning of the fever.
8	Antolisei and Angelini.	Tertiana anteponens (the same case as 7).	11 "	" " "	First irregular, then tertian.	1.5 c.c. intravenously. Blood taken at the beginning of the fever.
9	Gualdi and Antolisei.	Crescents (apyrexia).	13 "	Small ameboid; eight days later, crescents.	For ten days irregular, then eight days apyrexia and then recurrence.	2 c.c. intravenously.
10	Di Mattei.	Crescents.	(?)	Forms of the source.	Irregular.	
11	The same.	Quartan.	(?)	" " "	Quartan.	
12	The same.	"	18 days.	" " "	"	0.5 c.c. subcutaneously.
13	The same.	"	11 "	" " "	"	2 c.c. subcutaneously.
14	The same.	Small ameboid and crescents, irregular fever.	14 "	" " "	Irregular.	2 c.c. subcutaneously.
15	Calandruccio.	Quartan.	18 "	" " "	Quartan.	1 c.c. subcutaneously.
16	The same.	Crescents.	15 "	" " "	Irregular.	1 c.c. subcutaneously.
17	Bein.	Tertian.	12 "	" " "	Quotidian.	2 c.c.
18	The same.	Tertian parasite, types of fever quotidian.	12 "	" " "	"	2 c.c.
19	Bein.	Quotidian.	9 "	" " "	Tertian.	2 c.c.
20	The same.	"	9 "	" " "	Tertian, then six days apyrexia, later quotidian. Relapse.	2 c.c.
21	Baccelli.	Quartan.	12 "	" " "	Quartan.	4 c.c. Small number of parasites found. Sporulation forms.
22	The same.	Tertian.	6 "	" " "	First irregular, then quotidian.	3 c.c.
23	Bignami.	Tertiana maligna.	6 "	" " "	Tertiana maligna.	Part of a drop subcutaneously.

TABLE I.—EXPERIMENTAL INOCULATION OF MALARIA.—(*Continued.*)

No.	OBSERVERS.	FORM OF PARASITE AND TYPE OF FEVER IN THE SOURCE.	INCUBATION.	FORM OF PARASITE IN THE PERSON INOCULATED.	TYPES OF FEVER IN THE PERSON INOCULATED.	AMOUNT OF BLOOD INJECTED. REMARKS.
24	The same.	Tertiana maligna.	10 days.	Forms of the source.	Tertiana maligna.	The same.
25	Mannaberg.	Tertian.	21 "	" " "	Tertian.	0.2 c.c. of centrifugated blood; from the time of the paroxysm; corpuscular sediment subcutaneously.
26*	Celli and Santori.	Quartan.	25 "	" " "	Quartan.	4 c.c. subcutaneously. (Previously treated with horse-serum.)
27*	The same.	"	25 "	" " "	"	4 c.c. subcutaneously. (Previously treated with buffalo serum.)
28*	The same.	"	25 "	" " "	"	4 c.c. subcutaneously. (Previously treated with cattle serum.)
29*	The same.	Estivo-autumnal fever with small parasites.	30 "	" " "	(?)	1.5 c.c. subcutaneously. (Previously treated with horse-serum.)
30*	The same.	Estivo-autumnal fever with small parasites.	6 "	" " "	(?)	1.5 c.c. subcutaneously. (Previously treated with buffalo serum.)
31*	The same.	Estivo-autumnal fever with small parasites.	17 "	" " "	(?)	1.5 c.c. subcutaneously. (Previously treated with cattle serum.
32	Bastianelli and Bignami.	Tertiana maligna.	3 "	" " "	Irregular.	2 c.c. Taken at the close of the paroxysm, containing a considerable number of parasites.
33	The same.	Tertiana maligna.	4 "	" " "	"	5 c.c. taken at the close of the paroxysm; parasites scanty.
34	The same.	Pigmented ameboid parasites. Type of fever (?).	5 "	" " "	Irregular summer tertian.	0.75 c.c.; parasites scanty.
35	The same.	Pigmented and non-pigmented ameboid parasites.	4 "	" " "	Irregular.	0.20 c.c., containing a large number of parasites.

Table II shows the relations between the varieties of parasites and the different types of fever.

3. Blood examinations continued through weeks and months on

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* In cases 26–31 attempts were made to immunize the person inoculated by means of different sera, and in some of these experiments, as a consequence, no attention was paid to the type of fever.

malarial patients exposed to no new infection showed that the repeatedly renewed generations of parasites always belonged to the same species. Such investigations were carried on especially by Calandruccio and di Mattei. For instance, in the case of a triple quartan, the blood was examined daily for months and always showed only quartan parasites; in two patients showing crescents the blood was examined for two and six months respectively and no other parasites than those of the second group found.

Livio Vincenzi observed for months several cases of infection with parasites of the second group without seeing any forms other than the small ameboid ones.

Similar experiences, even if not extending over such a long period, may be had by any one who is occupied with the study of malarial blood.

It need scarcely be mentioned that the parasites do not modify their forms even when the patient changes his place of habitation. I see frequently, in Vienna, patients coming from the severe malarial regions of the south infected with parasites of the second group. In spite of a long sojourn on a foreign soil free from malaria these parasites, which are never observed autochthonously in Vienna, do not change their form, but remain the same for weeks and months.

We cannot, therefore, attribute an influence in the transformation of the parasitic forms to the climate, or even to the individual constitution, as Laveran insists.

4. In reference to the difference in the parasites and the types of fever according to the season, we find that the parasites of the first group (especially those of the common tertian), with their typical intermittent fever, play their rôle in the spring, and that the parasites of the second and their accompanying fever appear as a primary infection in summer and autumn.

In reference to the geographic distribution, we observe that in the southern and tropical malarial regions the parasites of both the first and second group occur, though even here with a predominance of the former in the spring months, and of the latter in the second half of the year; while in northern countries the parasites of the second group and the fever associated with them occur exclusively in severe malarial regions, and then only at the height of summer. The great majority of places in northern countries show only the parasites of the first group, with their typical fever.

During my ten years' investigation of this subject I have seen not one single case of malaria with parasites of the second group, in which the infection occurred in Vienna. Cases of this kind were always introduced, usually from Hungary, Rumania, Servia, Croatia, Dalmatia, Italy, or the tropics.

Moreover, the localization of the malarial virus can be carried still further. It was noticed, even by the old clinicians, that certain types of fever, like tertian and quartan, were associated with definite places. Though this is not an absolute rule and types usually occur mixed, the fact that a geographic separation of types can occasionally be made is of considerable significance.

In this regard we have a remarkable observation from Trousseau. He says: "Le type semble bien plus tenir à la nature du miasme, et pour mieux dire, à la localité qu'il infecte, qu'à des conditions inhérentes à l'individu, qui en subit les atteintes."

In support of this assertion Trousseau adds that in Tours only tertian fever occurs, and that the quartan fever observed there was always introduced and usually from Saumur, which, like Tours, lies on the left bank of the Loire. For instance, at one time 14 soldiers came to Tours from Saumur, 9 of whom, after several days, developed quartan fever. They had evidently acquired the disease in Saumur, for at the time there was exclusively tertian fever in Tours.*

I can report a similar manifestation in Vienna. In the last ten years I have seen develop here exclusively common tertian fever. The four cases of quartan which I had the opportunity of studying were all from other places. I think, therefore, that it is not unreasonable to say that, at the present time, the ordinary tertian fever with its corresponding parasite is the only one that occurs in Vienna.

These facts cannot be explained, or at most very unsatisfactorily, by the theory of polymorphism. Where can we find an analogy for the statement that a microbe would show a different form in southern and northern countries and different stages of development in spring and summer.

Laveran's assumption that the cachexia makes a nutritive soil on which the crescents can develop contradicts daily experience; for the crescents are present long before traces of the cachexia occur, and again an obstinate fever caused by parasites of the first group may lead to cachexia without a crescentic organism being seen.

All these phenomena are readily explained by the theory of multiplicity of parasites.

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* In his most recent work Laveran endeavors to throw doubt on this assertion of Trousseau by quoting contrary communications from two physicians of Tours and Saumur; yet we cannot without reason refuse to credit the absolutely definite assurance of Trousseau.

TABLE II.—PARASITES AND TYPES OF FEVER.

TYPE OF FEVER.	SPECIES OF PARASITES CAUSING IT.
Quartan	Only by one generation of quartan parasites.
Tertian	1. By one generation of common tertian parasites. 2. By one generation of malignant tertian parasites.
Quotidian	1. By one generation of quotidian parasites. 2. By two generations of tertian parasites (with twenty-four hours' interval). 3. By three generations of quartan parasites (with twenty-four hours' interval).
Continued	1. By several generations of malignant tertian parasites. 2. By several generations of quotidian parasites. 3. By quartan parasites and common tertian parasites, if more than three or at least two generations are present (very rare).
Irregular	1. By several generations of quotidian parasites. 2. By several generations of quartan and tertian parasites, at intervals of twenty-four hours after one another. 3. By the occurrence of different species in the blood; in other words, a mixed infection.

POSITION OF MALARIAL PARASITES IN ZOÖLOGY.

Nomenclature.—The classification of malarial parasites from a zoölogic standpoint did not at first meet with decided success, inasmuch as they were placed by some observers in the class of the sporozoa, by others in that of rhizopods. Yet now, as the outcome of the establishment of a sexual and an asexual cycle, as in the coccididæ, the conclusion that they belong to the sporozoa, like similar parasites in the lower animals, has been established, and it seems to us that this classification will probably be the final one. Among those who adopted this classification before our present standpoint was reached may be mentioned Metschnikoff, Danilewsky, and Labbé. The last recommended the subclassification of sporozoa (gregarinidia, coccidia, myxosporidia, sarcosporidia) into two further divisions, namely hemosporidia and gymnosporidia, and placed the malarial parasites of man in this last subdivision. The principal characteristics of the gymnosporidia are, according to Labbé: Complete intraglobular cycle of life; ameboid structure, even in the adult stage; reproduction, either by gymnospores within the blood-corpuscle, without the formation of a cystic membrane, or by simple intraglobular division. Malarial parasites of man would then be placed in the genus *Hæmamœba*.

Corresponding to the discordant views as to the nature of the malarial parasite, numerous scientific appellations have been proposed for it. We will mention some of them:

1. Oscillaria malariæ (Laveran), later repudiated by the author himself.
2. Hæmatozoön malariæ (Laveran).
3. Hæmatophyllum malariæ (Metschnikoff).
4. Plasmodium malariæ (Marchiafava and Celli).
5. Hæmatomonas malariæ (Osler).
6. A. Hæmamœba
    malariæ (quartan).
    vivax (tertian).
    præcox (pigmented quotidian).
    immaculata (unpigmented quotidian).

   B. Laverania malariæ (order of crescents, Grassi and Feletti).

Of all these names, only one has been adopted, and that the least appropriate. This is the name plasmodium, bestowed by Marchiafava and Celli on the small non-pigmented young ameboid forms of estivoautumnal fever. It is consequently contrary to the meaning of these investigators, when, for instance, a full-grown organism or a crescent is designated a plasmodium. That this name was chosen inaptly, even for the small ameboid organisms to which it was originally applied, is conceded by the authors themselves.

Zoölogists designate, by the name plasmodium, those organisms which originate from the running together of numerous amebæ, each one of which preserves its nucleus. In a scientific sense, therefore, a plasmodium is a plasma mass containing many nuclei. This, as is well known, does not apply to the malarial parasite, containing, as it does, almost without exception, only one nucleus. Moreover, this name is not available, because we are dealing not with one species, but with many, every one of which requires a special name in order to make it definite. Some of the other designations were undoubtedly chosen both rationally and appropriately, and might, therefore, be preserved. Yet I avoid choosing one from among them, because I am of the opinion that with the complete understanding of the place in zoölogy occupied by the parasites, it will be the duty of the special scientists to agree on a final name.

Until then we will continue to use the general expression, "malarial parasite." As will be seen later on, this is easily employed, even in the explanation of details. The author is complimented by the fact that a considerable number of German and foreign investigators have adopted his nomenclature, which is a good sign of its practicability.

SPECIAL CHARACTERISTICS OF THE INDIVIDUAL SPECIES OF PARASITES.*

We divide the malarial parasites as follows:

1. Malarial parasites that sporulate but do not form syzygies (*i. e.*, crescents):
    - (*a*) Quartan parasites.
    - (*b*) Tertian parasites.
2. Malarial parasites that sporulate and form syzygies (*i. e.*, crescents):
    - (*a*) Pigmented quotidian parasites.
    - (*b*) Non-pigmented quotidian parasites.
    - (*c*) Malignant tertian parasites.†

1. Malarial Parasites that Sporulate Without Forming Syzygies.—The course of development of the two species of parasites belonging to this group has been described by Golgi, and, omitting isolated details, we will not deviate from this description.

The Quartan Parasite.—The quartan parasite (Plate IV) completes its development (from the spore to sporulation) in three times twenty-four hours.

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* This and the following sections are, with slight changes, taken from my monograph, "Die Malaria-Parasiten."

† Grassi and Feletti have proposed the following division:

1. Genus Hæmamœba—
    Hæmamœba malariæ.
    Hæmamœba vivax.
    Hæmamœba præcox.
    Hæmamœba immaculata.
2. Genus Laverania malariæ.

Grassi and Feletti proceed on the assumption that crescents do not originate from all species of small parasites, but from only a definite species, the principal characteristic of which is that it does not sporulate, but instead forms crescents. Carrying out this assumption, they make two genera, *Hæmamœba* and *Laverania*. They place in the first the ordinary quartan and tertian parasites and the pigmented and non-pigmented quotidian parasites. In the genus *Laverania* they put only one species, the Laverania malariæ, consisting only of crescents and causing the mild, irregular fevers.

Grassi and Feletti explain the fact that the great majority of cases show crescents in addition to the small sporulating forms by declaring these cases to be mixed infections. I cannot accept this division of Grassi and Feletti, since I believe with Canalis and the Roman school that the small parasite may either sporulate or form crescents. Grassi and Feletti gave the following reasons for their opinion: 1. In six cases of severe pernicious fever they found five times Hæmamœba præcox and Laverania; in one case, the Hæmamœba præcox alone. The first five they considered mixed infections, the last one, a pure infection.

2. In three cases of summer fever showing ameboid organisms (of undetermined character) and crescents they punctured the spleen at the beginning of the parox-

DESCRIPTION OF PLATE IV.

A, Figs. 1 to 22. Stages of development of the quartan parasite.

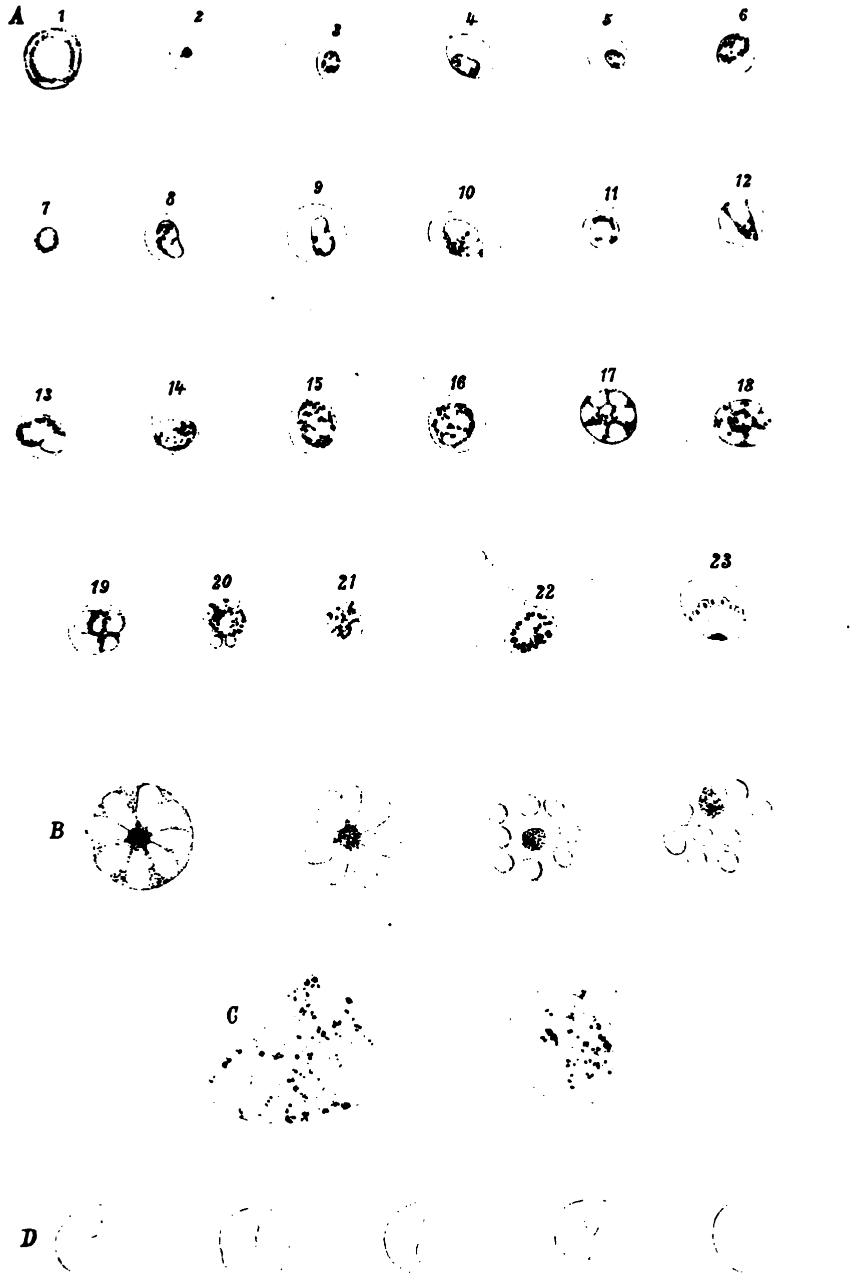
Fig. 23. Rare sporulation form (after Canalis).

B. Schematic sporulation of quartan parasite (after Golgi).

C. Leukocytes containing melanin.

D. Various vacuolization of the erythrocytes.

PLATE IV.



In its young condition it appears as a non-pigmented organism, looking like a small clear speck, on or in the infected blood-corpuscle. It possesses a slow ameboid movement which is usually only visible on a warm stage.

The parasite remains at this stage of development twelve to twenty-four hours, increasing only a little in size. A deposition of pigment then takes place in the outer layers of the parasite, consisting of quite large, dark lines and granules which show no movement. With increasing pigment-formation the parasite loses the slight power of movement manifested in the beginning and appears as a spheric, completely immotile body, filling from one-third to one-half the red blood-corpuscle. It has a sharp contour and its substance is quite refractive.

The parasite grows gradually and slowly, until finally, under normal circumstances, it reaches the size of the red blood-corpuscle, when, especially in unstained preparations, nothing more of the red blood-corpuscle is visible.

It now prepares itself for sporulation, in that the pigment-granules clump themselves compactly in the center of the organism and a spoke-like arrangement appears at the periphery of the plasma, which

ysms many times (number not stated) and found only numerous crescents, but no sporulation forms, as should have been the case according to Marchiafava and Celli.

3. These cases without sporulation forms (that is, without Grassi and Feletti's Hæmamœba præcox and immaculata) were never pernicious, but always mild.

Some of the arguments against their position are: 1. That on careful investigation crescents are found in association with the small parasites in so large a majority of cases that it is difficult to believe that they are all mixed infections. 2. That the crescents usually appear in the blood only some time after the beginning of the infection, which would indicate that they arise from the ameboid organisms originally present. 3. That a constant connection between the severity of the clinical course and the number of crescents does not exist. 4. That the number of crescents is, as a rule, so much smaller than that of ameboid organisms that we cannot regard them as obligate forms of development.

As far as I know, Livio Vincenzi was the only one who adopted the opinion of Grassi and Feletti, on account of observing several cases of estivoautumnal fever which showed only ameboid organisms and never crescents, though the observations were continued over months. Among these cases there were several of septan type.

According to my explanation of the origin of crescents, these isolated cases are easily explained by assuming a failure of double infection in the blood-corpuscle, and, as a result, no possibility of copulation. Thayer and Hewetson divide the parasites as follows:

1. Parasites of tertian fever.
2. Parasites of quartan fever.
3. Parasites of estivoautumnal fever (Hæmatozoön falciparum, Welch)

From their experience they believe that the small parasites of estivoautumnal fever are not separable into different species. Van der Scheer divides them into two species, large and small parasites.

gradually extends to the center. These radial lines becoming gradually sharper, divide the parasite into a varying number of segments, usually not exceeding ten.

These lines broaden into grooves until finally the segments previously outlined become separated from one another as oval organisms ("daisy form," Golgi). In each of these a circumscribed, glistening speck usually appears which represents the nucleolus. This gives to the segments the character of independent organisms. The fully formed spores are now so closely connected with one another that pressure on the preparation may completely separate them; and even without this external violence the spores break apart, probably as a result of their growth and the rupture of the thin membrane surrounding them. This completes the life-cycle of the parasite. The remaining clumps of pigment are carried away by the leukocytes as dead matter.

The segmentation of the parasites occurs immediately before and during the fever paroxysm. Ordinarily we see that the first sporulation forms about three hours before the outbreak of the chill, at which time there may already be considerable elevation of temperature.

The sporulation forms may vary more or less in their shape and size. For instance, it sometimes happens that sporulation may occur at a time when the parasite has not yet reached the size of the red blood-corpuscles. Under these circumstances the number of spores is usually less—about four to six. Canalis described an interesting sporulation form of fan shape, produced by the clumping of the pigment eccentrically. The nucleolus may be invisible. Jancsó and Rosenberger assert that they have observed flagella on the spores, by the aid of which they moved about.

The infected red blood-corpuscles remain unaltered in shape and size, or become somewhat smaller without change of form. The color of these shrunken, though round corpuscles is darker than that of the non-infected. The infected corpuscles are not at all or only slightly decolorized—in fact, as already mentioned, they may become somewhat darker. In this they are especially differentiated from the corpuscles infected with tertian parasites.

The following findings in quartan fever show the different stages of the parasites corresponding to the different stages of a fever cycle:

Twelve hours after the paroxysm: Small parasites, showing sluggish ameboid motion or immotile, containing but little pigment, or non-pigmented, and situated on or within the red blood-corpuscle.

Twenty-four hours after the paroxysm: Isolated organisms show at the periphery a few pigment-granules, others none at all. Their size is about one-sixth to one-fifth that of the red blood-corpuscle.

Forty-eight hours after the paroxysm (twenty-four hours before the subsequent paroxysm): The parasites take up half or two-thirds of the red blood-corpuscle; they are markedly pigmented, usually round, and immotile. The pigment likewise shows no motion.

Sixty hours after the paroxysm (twelve hours before the paroxysm): The parasites fill the red blood-corpuscle so completely that only a small margin recognizable by its color remains.

Sixty-six hours after the paroxysm (six hours before the paroxysm): In many instances nothing more can be seen of the margin of the red blood-corpuscle. The pigment is radially arranged, and in some corpuscles, loosely clumped. In isolated parasites signs of beginning sporulation may be perceived.

Sixty-nine hours after the paroxysm (three hours before the paroxysm): Individual organisms are in the act of sporulation; many others show clumped pigment and the signs of beginning sporulation.

As an example of the connection between the stages in the fever and the development of the parasite I give here, in an abridged form, an instance of simple quartan:

R. G., aged twenty-two, was admitted on January 26, 1893, to the first Medical Clinic (Prof. Nothnagel). He first manifested quotidian intermittent in September, 1892; he had a relapse in November of the same year. He had now been suffering since December 28 with a new relapse, the paroxysm of which occurred every second or, more frequently, every third day.

The examination discovered numerous râles over both lungs, a systolic murmur at the apex of the heart, and an easily palpable tumor of the spleen, which extended 3 cm. beyond the border of the ribs.

Blood examination—January 26, 11 A. M.: Temperature, 37°. Large numbers of parasites filling completely the red blood-corpuscles. In many the pigment was clumped and their substance divided into four to six segments. Many of these segments showed a clear speck. The infected blood-corpuscles were not swollen. Simple quartan was diagnosticated, and the paroxysm was announced as immediately at hand. As a matter of fact, at 2.45 P. M. there was a violent chill and the temperature at 4 P. M. was 39.6°. In the blood taken during the paroxysm large numbers of organisms in the act of sporulation were found.

January 27: Normal temperature. The blood showed quite a number of small pigmented parasites, from about one-sixth to one-fifth the size of a blood-corpuscle.

January 28: Normal temperature. In every twentieth microscopic field an infected blood-corpuscle. The parasites contained considerable pigment, lying immotile at the periphery. The size of the parasites was three-fifths to four-fifths that of a blood-corpuscle. The blood-corpuscles were neither enlarged nor decolorized.

January 29: Day of paroxysm. 10 A. M.: Temperature, 36.8°. A parasite was found in about every twentieth microscopic field, taking up almost the whole of a corpuscle. The majority contained pigment clumped at the center and showed beginning sporulation; in a few the sporulation was almost complete. Number of spores, nine.

12 M.: Temperature, 37.5°.

2 P. M.: Temperature, 39.6°. Beginning of the chill.

4 P. M.: Temperature, 40.5°. A small number of sporulation forms, some of which were in the act of breaking up, and a few quite young parasites with scanty pigment.

We observe sometimes a lively activity of the pigment in large free spheric organisms that probably remain sterile.

The protrusion of flagella is seldom seen. The course of development is more regular than in the other species, both in relation to the duration of development and the progress in growth of the single individuals. Moreover, sporulation forms are more frequently found in the peripheral blood, since the whole cycle of development usually takes place within the vascular system.

Finally, the development of the parasites belonging to one generation or series *pari passu* makes it relatively easy to recognize the presence of several generations and judge of their age.

Tertian Parasite (Plate V).—Its duration of development requires forty-eight hours. When seen first in the corpuscle, it appears as a small (1 to 2 μ in diameter), somewhat clear spot. In this stage it is non-pigmented or contains only extremely fine pigment-dust. It possesses a lively ameboid movement, readily visible at the room-temperature for a long time (about an hour) after the removal of the blood. This consists not in a slight change of form, but in the actual protrusion of pseudopodia in different directions, which are soon drawn in to make room for another formation. The parasite remains at this stage (Golgi's first phase), growing gradually for about twenty-four hours. More and more pigment in the form of fine granules and lines collects, particularly at the periphery of the plasma, where it usually manifests a lively swarming movement. The greater the amount of pigment, the older the parasite and the less its ameboid movement. Still we frequently see, on apyretic days, pigmented organisms (often curiously branched on account of their pseudopodia) which continue to change their form actively, at a time when they are more than half the size of the corpuscle.

Simultaneously changes are occurring in the infected red blood-

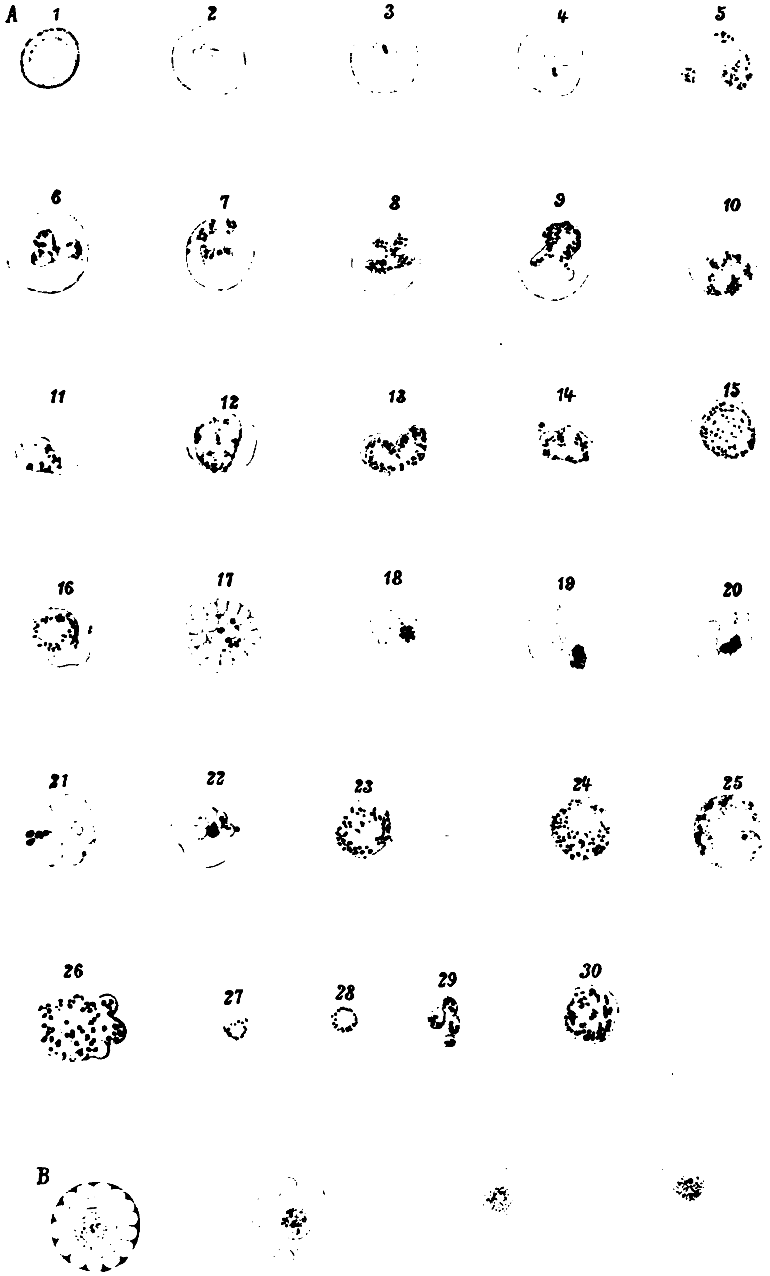
DESCRIPTION OF PLATE V.

A, Figs. 1 to 22. Stages of development of the tertian parasite (Figs. 17 and 18, after Thayer and Hewetson).

Figs. 23 to 29. Hydropic degenerated malarial bodies.

B. Schematic sporulation of the tertian parasite (after Golgi).

PLATE V.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corpuscles. These lose in color, look pale in comparison with the non-infected ones, and often increase in size.

Sporulation takes place after a life-cycle of about forty-eight hours. At this time the organism has lost its motility, is almost or quite the size of a normal blood-corpuscle, its host is enlarged and almost completely decolorized; and the swarming of the pigment is suspended. According to Golgi, segmentation may occur in three ways:

The most common form, confirmed by all observers and which I have often seen, is as follows: While the pigment concentrates itself in the center of the organism in a thick clump, the plasma of the parasite breaks up into 15 to 20 round, strongly refractive small spheres (spores). These sometimes arrange themselves regularly in two concentric rows,—Golgi's "sun-flower,"—but usually irregularly, recalling rather the appearance of a grape or a mulberry. Yet observing them, as we do, spread out between slides, it is not impossible that the original regular form may have been destroyed by the mechanical violence which can never be entirely avoided in making the preparation, especially since the bodies are loosely attached to one another as a result of the breaking up into spores.

The spores of the tertian parasite are round and smaller than those of the quartan. In the recent condition no structural details are usually visible, though now and then a glistening kernel, the nucleolus, is seen.

We will pass over Golgi's other two methods of segmentation, since it is likely that they are only phenomena of degeneration.

Yet it may be worth while mentioning a not infrequent form of sporulation to which Celli and Guarnieri called attention. In this segmentation takes place without concentration of the pigment, or with the pigment concentrated in two heaps instead of one.

The most characteristic feature in the sporulation of the tertian parasite is the large number (15 to 20) of small round spores. After the spores have broken away from one another, the pigment becomes the prey of the leukocytes.

As in quartan, so also in tertian, fever the act of sporulation corresponds to the paroxysm of fever. So, too, about three hours before the commencement of the chill, a gradual rise in temperature occurs, and, corresponding to it, isolated organisms in the act of sporulation are found in the blood; though, naturally, they are most numerous at the time of the chill or the beginning of the hot stage.

Still it must not be forgotten that sporulation forms may be sought in vain in the blood of tertian fever, on account of the last stages of development occurring in the internal organs. We will meet this peculiarity in a marked degree in the parasites of the second group.

Moreover, now and then an isolated sporulation form is found at a time quite remote from a paroxysm. In this case it is possible that there is in the blood a second feebler generation which sporulates at another time, but in too small numbers to cause a paroxysm.*

Again, not all the sporulation forms of the tertian parasites present the typical picture which Golgi traced out for them, but deviations from the normal occur, which we should be able to recognize. For instance, it not rarely happens that the organisms sporulate at a time when they take up only a small portion of the red blood-corpuscle (see also Anticipating Tertian). They then form a considerably smaller number of spores and resemble the sporulation forms of the pigmented quotidian parasites, from which they are differentiated by the greater amount of pigment and the larger size of the individual spores. In these cases the general blood-picture is important.

The microscopic finding in a simple tertian is about as follows:

One to twelve hours after the paroxysm: Very small, slightly pigmented forms, showing active ameboid movement, attached to or partly within the red blood-corpuscle.

Twelve to twenty-four hours after the paroxysm: Somewhat larger forms, still actively ameboid, containing very fine pigment-dust and filling about one-third of the blood-corpuscle. The infected corpuscles are pale and enlarged.

Twenty-four to thirty-six hours after the paroxysm (twenty-four to twelve hours before the subsequent paroxysm): The organisms fill two-thirds to four-fifths of the pale, enlarged blood-corpuscles, are often of very irregular shape, and change their form very slowly; though the now numerous enlarged pigment-granules are in lively motion that shakes even the parasites themselves.

Thirty-six to forty-eight hours after the paroxysm (twelve to no hours before the paroxysm): Large round forms, having almost the diameter of a red blood-corpuscle; in one the pigment in motion, in another, at rest; beginning and complete sporulation forms.

As an illustration of the correspondence between the development of the parasite and the course of the fever we detail the following case of simple tertian fever:

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* Golgi makes the assertion in relation to quartan fever that he has seen sporulation forms in several cases outside of a paroxysm; in these cases the body-temperature was elevated, though insensibly to the patient.

K., age twenty, had the first paroxysm on August 21; other paroxysms occurred on the twenty-third and twenty-fifth of the same month, each time at 11 A. M. The course of the paroxysm was entirely typical: chill, fever, sweating.

August 25, 5 P. M.: Temperature, 40.5°; the chill took place at 11 A. M.

Blood examination: 1. Quite numerous large forms, taking up half of the hypertrophic and decolorized red blood-corpuscles, and filling the normal ones entirely. 2. Several in the act of sporulation in the form of clusters. Numerous beginning sporulation forms. 3. Isolated, quite small, non-pigmented ameboid organisms (very young forms), a further stage of the spores that originated at the beginning of the paroxysm (about 11 A. M.), consequently about six hours old.

August 26, 10 A. M.: Temperature, 36°.

Blood examination: 1. Numerous pigmented ameboid organisms, filling one-fifth to one-fourth of the red blood-corpuscle. 2. Isolated large forms containing considerable pigment (sterile forms from the day before).

5 P. M.: Temperature, 36.3°.

Blood examination: 1. Numerous pigmented, endoglobular forms, often strikingly branched, filling one-fourth to one-half of the blood-corpuscle. 2. Isolated large, dropsical forms.

August 27, 9 A. M.: Temperature, 37.3°.

Blood examination: 1. Very numerous, large forms, filling entirely or one-half of the corpuscle; many of the infected blood-corpuscles swollen and decolorized. 2. In isolated large organisms the pigment at rest (beginning sporulation).

At 11 A. M.: Temperature, 39.5°, chill, etc.

From this example it would be easy to construct another for a double tertian, in which the paroxysms took place at the same or different hours of the day.

In illustration of this complicated condition we detail the anamnesis of a case of tertiana duplex, together with its microscopic data.

F. W., aged nineteen, a glass-worker, has had paroxysms for the last fourteen days, which, in the beginning, occurred every second day, later daily. Yesterday (August 11) the attack occurred at 11 A. M.; to-day (August 12), at 3 P. M. At 5 P. M., temperature, 39.2°; spleen evidently palpable; pains in the limbs.

Blood examination: 1. Large number of pigmented organisms filling entirely the blood-corpuscles. 2. Large number of pigmented parasites in lively ameboid movement, filling half of the corpuscle. Numerous free pigmented spheres; in the blood-corpuscles, frequent torn forms (fever forms, see below). 3. Sporulation forms not found.

August 13, 11.15 A. M.: Beginning chill; temperature, 38.2°.

Blood examination: 1. An enormous number of sporulation forms, some regularly, others irregularly, arranged. Number of spores, about 14; in some of them a nucleolus evident. 2. Quite numerous ameboid, slightly pigmented forms, filling about one-third of the corpuscle. 3. Several large forms with flagella (one with five flagella).

5 P. M.: Temperature, 37.5°; profuse sweating.

Blood examination: 1. Isolated large forms, some with pigment in motion, others with pigment coagulated, as it were. 2. Numerous lively, slightly pigmented forms, filling one-third to two-thirds of the red blood-corpuscle. 3. Numerous quite small, actively ameboid forms, non-pigmented or containing only the finest granules of pigment. 4. Sporulation forms are no longer to be seen, etc.

It is at once evident that we had to do in this case with a double tertian (*i. e.*, false quotidian) due to two generations of parasites. From the last observation it might appear that three generations were seen, yet on reflection it is clear that the isolated large forms referred to under 1 were only the remains of that generation which caused the paroxysm six hours previously. The organisms from the spores of that generation are represented by the small ameboid forms (No. 3).

It is essential to bear in mind, therefore, other factors besides Golgi's outline, in order properly to appreciate the blood-picture. In the first place, in a strict sense, we never see only one generation of parasites. If this were the case,—in other words, if all the parasites which we reckon in general as belonging to the one generation, were exactly the same age to the minute,—all of them would sporulate at the same time and break up at the same time, while, as a matter of fact, the parasites of the same generation vary six to eight hours in age. It is impossible, however, to separate them, because the necessary limits to such a separation are wanting. Still, this separation is not at all necessary, for we need consider only all those parasites which produce a fever paroxysm as belonging to one group or one generation, and whether they are of the same age or manifest differences of hours is not important.

The fact that the individuals of one generation do not sporulate at the same moment, but following one another at short intervals, causes the fever paroxysm to last not a few minutes, but several hours—often even half a day.

This difference in the age of the parasites of one generation naturally produces differences (even though they may not be striking) in size, form, and other characteristics; still it would be wrong to let those influence our conclusions.

Another series of organisms that tend to complicate the blood-picture are the "fever forms." These are fragmented parasites which are frequently found free in the plasma, though often, too, in the red blood-corpuscles. They are usually round, and several are often attached together. A confusion with sporulation forms is scarcely possible, since they are irregularly pigmented and differ in size.

Flagellate organisms are frequently observed among the tertian parasites soon after the removal of the blood.

[The characters of the sexual forms in the blood are described in the appendix to this article (see p. 123).—Ed.]

The swelling and decolorization of the red blood-corpuscles, though very frequent, are not constant. These varying conditions may be seen in Plate V. Bastianelli and Bignami occasionally observed, even in tertian fever, shrunken, brassy-looking blood-corpuscles (globuli rossi ottonati) similar to those seen in quartan fever. I have never observed these "brassy corpuscles" in tertian fever, although I have had the opportunity of studying a great number of cases. They seem, therefore, to be exceptional occurrences.

Nor can I confirm another statement, made in the same paper, namely, that premature sporulation forms containing from five to ten spores are frequently seen in anticipating tertian.

If we apply Golgi's law to this not uncommon variety of tertian fever, we must assume that the tertian parasites may, under certain circumstances especially favorable to their development, reach maturity some hours earlier than usual, or thrive from the beginning with more vital energy so as to multiply sooner than in forty-eight hours. As far as the number of spores and the size of the sporulation forms were concerned, I found no difference from the ordinary tertian. Still I do not intend by this to deny Bastianelli and Bignami's observation. On the contrary, I believe that this is worthy of attention and further investigation.

I know of no observations that have been made so far on the much rarer postponing tertian.

The structural relations in the development of the tertian parasite are shown in Plate VII.

2. Malarial Parasites that Sporulate and Form Syzygies.—To this group belong the small parasites investigated by Marchiafava and Celli. They are differentiated biologically from the parasites of the first group in that the latter show only direct sporulation, the former direct sporulation and crescent formation.

Clinically, these parasites produce a fever that relapses obstinately, leaves behind an anemia which is cured with difficulty, and gives rise to other pernicious phenomena.

The paroxysms often lack the fixed character of those occurring in the milder intermittent, and the chill especially may be wanting. The patients give throughout the impression of severe illness. They complain principally of prostration, pain in the limbs, headache, and loss of appetite.

In mild cases a more evident type is usually recognized. This may be quotidian or tertian (quartan does not occur), though again it may be distorted and difficult to analyze. Such continued and remittent fevers are produced by the rapid evolution of several generations of parasites.

Sporulation occurs almost exclusively in the internal organs, as pointed out by Marchiafava and Celli. The reason for this is so far entirely unknown. The relapse takes place eight to fourteen days after the previous paroxysm.

The Pigmented Quotidian Parasites.—We have several times mentioned that we must thank the valuable work of Marchiafava and Celli for our knowledge of the small parasites occurring in pernicious fevers. Yet our division of these into pigmented and non-pigmented is not in the sense of the Roman observers. They have always insisted that the pigmentation depends only on the duration of life, and that between them, therefore, there is no specific difference, while I believe that the division proposed by Grassi and Feletti into two species should be accepted, because a parasite that is always non-pigmented was found by Grassi in birds, and the slightly pigmented parasites in certain birds have been recognized as a well-defined species. Inoculation experiments in man similar to those mentioned for the quartan and tertian parasites have not yet been made with these two species. Moreover, we would not expect such experiments to give the clear results seen in the mild types, because mixed infection with the two species seems to be frequent. Finally, the circumstance that the pigmented forms may be wanting in the peripheral blood, while present in the internal organs, would add to the confusion.

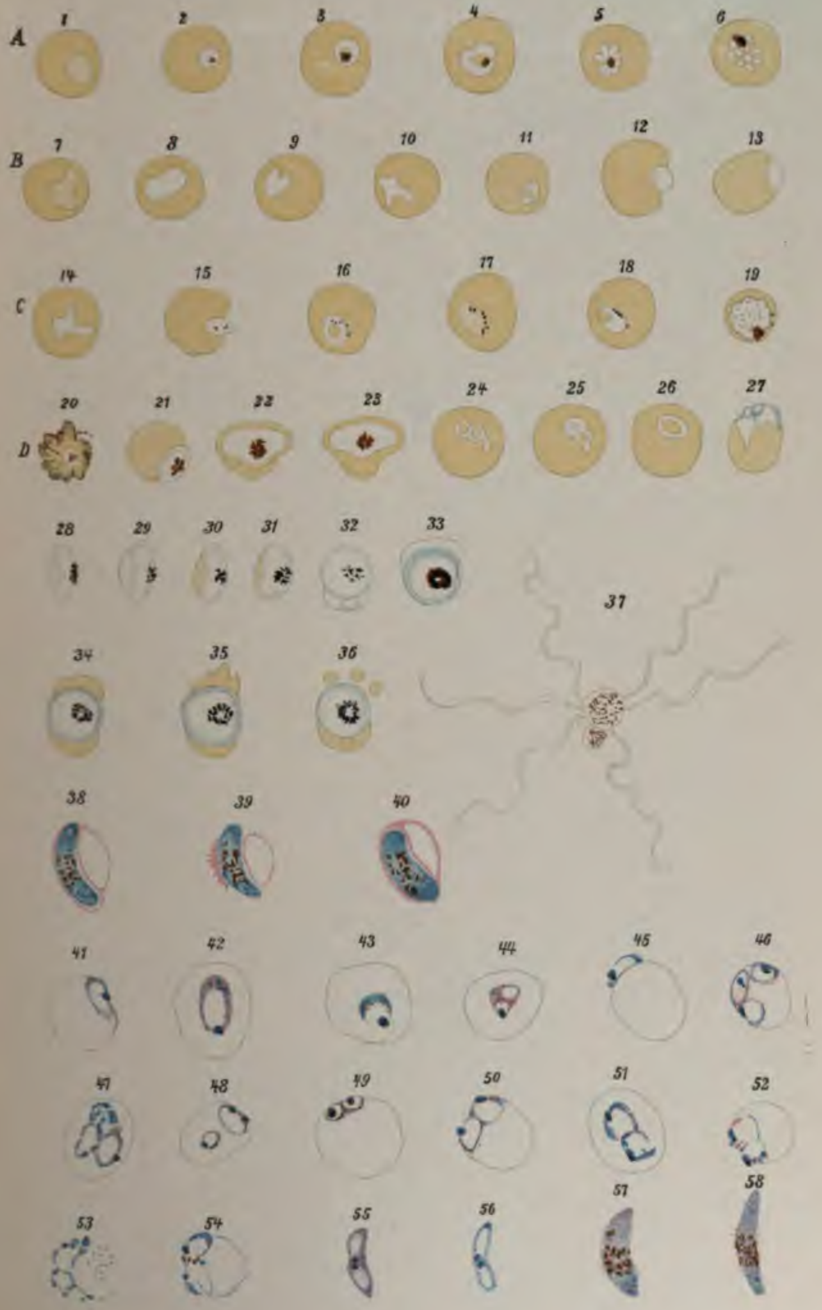
The pigmented quotidian parasite describes its cycle of development in twenty-four hours. It begins its existence, like all varieties, as a very small, non-pigmented organism. After its escape as a spore it lives a short time in the plasma and then attaches itself to a red blood-corpuscle.

These small organisms are actively ameboid, and it is this activity that attracts the attention of the observer. In general (as long as they do not go over into the ring form, with its condition of rest) they are optically so similar to the substance of the red blood-corpuscle that they may easily be overlooked by the inexperienced. Their contour is very delicate, their color a little paler than that of the red blood-corpuscle. Some of the organisms retain their activity under the microscope at room-temperature for a considerable time, —an hour or even longer,—while others cease their motion soon after

DESCRIPTION OF PLATE VI.

A, Figs. 1 to 6. Pigmented quotidian parasites.
B, Figs. 7 to 13. Unpigmented quotidian parasites.
C, Figs. 14 to 19. Malignant tertian parasites.
D, Fig. 20. Brass-colored erythrocytes.
Figs. 21 to 37. Crescentic bodies.
Figs. 24 to 26. Fusion of two ameboid parasites (copulation).
Fig. 27. Conjunction of two bodies.
Figs. 38 to 40. Stained crescents (by Romanowsky's method).
Figs. 41 to 58. Stained parasites of the second group.
Figs. 49 to 57. Formation of the crescents (conjunction of the bodies) (stained with hematoxylin after fixation by picric acid).

PLATE VI.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the removal of the blood (possibly even too in the circulating blood). When at rest, the organisms form very characteristic small rings, hyaline in appearance, with a red center, on account of which they are at once striking to the observer. Oftentimes the ring shows at one portion a small nodule, and then is appropriately compared to a signet ring. The ring not uncommonly contains one or several granules of a hemoglobin-derived substance—viz., melanin, which it has drawn from the blood-corpuscle.

It is sometimes possible to observe the manner in which these rings arise. If a homogeneous ameboid organism is observed for a long time, until it has ceased its motion and become round, a dark spot is seen suddenly to appear in its center. This speck undoubtedly originates by the thinning-out of the plasma and the shining through it of the substance of the red blood-corpuscle. This thinning-out of the parasite at its center may continue to actual perforation when the ring is made.

Observing such a ring with an open Abbé and deflected light, we can see that it makes a deep sharp furrow in the surface of the blood-corpuscle, which protrudes into the center like a finger in a ring. From this ring form the parasite may return to the ameboid form; this play often repeats itself several times under the eye of the observer.

The young ameboid parasites show extremely fine pigment-dust, often reddish in color. This is entirely at the periphery of the organism, and usually manifests slight movement. After the parasite has grown to about one-third the size of the red blood-corpuscle, the pigment collects in the middle or at the margin and the ameboid movement ceases. After concentration, the pigment remains at rest in dark clumps and the parasite breaks up into a few very small spores. The parasites sometimes, too, reach a considerable size, so that at the time of their sporulation they may fill a whole corpuscle.

As Marchiafava and Celli have proved in the mild cases of summer fever of intermittent, quotidian type, so, too, in these the concentration of the pigment and the sporulation occur simultaneously with the fever paroxysm. Those observers also discovered the sporulation forms of these parasites, and demonstrated that the sporulation does not take place in the peripheral blood, but in the internal organs. As a consequence, therefore, during the paroxysm, even in cases of severe infection, none at all or only a few segmentation forms are found in the blood from the finger, while large numbers are seen in the blood from the spleen.

The discovery, in the peripheral blood, of a number of large parasites containing pigment-clumps is a positive indication of the approach of a paroxysm. This is also true for the malignant tertian parasites. After the paroxysm the non-pigmented small rings are found.

The infected red blood-corpuscles frequently shrink and then assume the color of old brass. Marchiafava and Celli believe that the parasites inclosed in the "brassy corpuscles" are degenerated forms. On account of the structural staining, which shows the nucleolus deeply stained, I cannot support this view.

These infected shrunken blood-corpuscles may lose their color completely and become extremely delicate, veil-like, and wrinkled. The "brassy corpuscles" should not be confused by the inexperienced with the "morning star" or "halberd" forms. To differentiate them it is only necessary to remember that the parasite is always to be seen in the case of the "brassy corpuscle," being usually in the form of a small hyaline ring stamped on the "brassy corpuscle" in a manner which cannot be mistaken.

After the disease has existed for some days we see, in addition to the already described forms, others belonging to the order of crescents. These are: (1) The typical crescent-shaped bodies; (2) spindle-shaped forms, pointed at the ends (cigar forms); (3) spheres.

A detailed description of the morphology of these forms and mode of origin has already been given in previous sections.

In illustration of the connection between the clinical and microscopic phenomena of these cases the following history is reported:

K. St. has suffered daily for a week with paroxysms of fever which occurred about 4 P. M., and consisted only of a hot stage. The patient is very weak, unable to walk, and had to be carried to the hospital. Marked pallor, typhoidal condition. The teeth are dry, the papillæ at the tip of the tongue swollen, the posterior half of the tongue covered with a thick grayish coating. The spleen is evidently palpable. Pulse 110, dicrotic, tension normal. Two or three thin liquid stools daily.

August 4, 1892, 5 P. M.: Temperature, 38°.

Blood examination: 1. A few small ameboid, non-pigmented organisms. 2. A large number of melaniferous leukocytes.

August 5, 9 A. M.: Temperature, 37°.

Blood examination: 1. A very few organisms of medium size, filling one-fourth to one-third of the blood-corpuscle, and containing one clump of pigment. 2. Isolated "brassy corpuscles"; no melaniferous leukocytes.

4 P. M.: Temperature, 38.2°.

Blood examination: 1. Isolated, small pigmented organisms. 2. One crescent with concentrated pigment.

6 P. M.: 0.66 quinin.

August 6, 7 A. M.: 0.66 quinin.

10 A. M.: Temperature, 36.5°. Patient considerably prostrated, tongue dry and brown.

Blood examination: 1. Isolated crescents. 2. A moderate number of melaniferous leukocytes.

4 P. M.: Temperature, 35.4°; general condition as before.

From this time on no other paroxysms took place, and the condition, previously so threatening, improved rapidly.

In this case we must remark the disproportion between the small number of parasites, the slight elevation of temperature, and the severity of the other symptoms. The crescents appeared on the eighth day of the disease.

As mentioned previously, crescents, and the organisms belonging to this class, appear usually in the blood only some time after the beginning of the disease. Moreover, they are found there occasionally in association with isolated ameboid organisms even during the apyretic period. When these are seen in the blood of a patient, we can draw the positive conclusion that paroxysms of fever must have occurred a short time before. As long as the crescents and their spheres remain the only features of the blood, there is, as a rule, no fever. In fact, the Roman school holds that these organisms are incapable of causing fever, and that when paroxysms occur, endoglobular ameboid organisms must also be present. Marchiafava and Celli have seen cases with large numbers of crescents in the blood without rise of temperature. Other investigators have made similar observations. My own experience agrees with this for the great majority of cases, yet I must add that I have met several with moderate paroxysms of fever in which I have searched in vain for the ameboid organisms. It is naturally possible that these were present not in the peripheral blood, but only in the vessels of the internal organs; and I consider this assumption very probable. Nevertheless, from the standpoint of clinical medicine, these cases cannot be passed over, and I will, therefore, take occasion to detail a few from this category among the following histories. Still I can affirm that it is the rule for the fever to be wanting when crescents alone are present. Yet in spite of this the patient is frequently in a more or less cachectic condition and the lessened amount of hemoglobin and the decreased number of corpuscles in association with it improve slowly or not at all; in fact, sometimes become worse.

After the course of two or three weeks paroxysms of fever may again occur, accompanied by the invasion of young ameboid organisms.

The question at once proposes itself, What organism is to be considered the source of the infection latent for so long a time? The most ready answers would make the crescents responsible for the relapse, and this is not improbable. In order to make this probability certain it is necessary to demonstrate that crescents or spheres of that order may give rise to spores capable of developing into ameboid organisms.

As mentioned previously, Canalis believed that he observed sporeformation in several spheres. Unfortunately, he did not demonstrate, by nuclear staining, that the bodies were actually spores, and his assertions may, therefore, be questioned.

The early opinion of Celli and Guarnieri that the well-known "buds"

("Knospen") on the spheric organisms are spores is disposed of on account of the absence of nuclei. The statement of Grassi and Feletti that they found spore-forming spheres (of crescents) in the splenic blood is questionable, at least judging from the drawings which they made of these bodies.

Feletti recently observed on some crescents from one to eight nuclear-like bodies, which he considered to be gymnospores. I personally am not absolutely convinced of the sporulation of crescents, yet I can affirm that segmentation, as first described by Grassi and Feletti, undoubtedly occurs, and I consider it possible that this segmentation, during which the individual organisms assume a finely granular appearance, has a connection with reproduction, though it must be confessed that this cross-segmentation is a rare occurrence. [For further observation on this point, viz., parthenogenesis of gametes, see page 121.—ED.]

The statements in regard to the increase or decrease of the crescents in the apyretic intervals and in the course of a relapse are not in accord, for while one set of observers claim a diminution in number, others affirm an increase or no change. Personally I have seen no striking, or at least no regular, differences, for it happens that on one day numerous bodies of this class are found, and on the next day only isolated ones, without any alteration having occurred in the patient. Moreover, the observation of several writers that crescents are transformed into flagellate spheres more frequently at the time of the relapse than during the apyretic period I have not been able to confirm.

In stained preparations the young quotidian parasite shows similar characteristics to the young forms of the tertian and quartan organisms, possessing, like them, a nucleus, nucleolus, and plasma.

The Unpigmented Quotidian Parasite.—The occurrence of a malarial parasite that forms no pigment and that, therefore, sporulates in a non-pigmented condition has been proved by Marchiafava and Celli. This is one of the greatest contributions of these two active and tireless investigators as to the etiology of malaria. These non-pigmented parasites have since then been repeatedly observed by other investigators, as Marchoux, in Sénégal.

Excepting that they do not contain pigment, these parasites resemble so closely the pigmented quotidian parasites that we may omit a detailed description of them. In the young condition they show the same ameboid movement. They complete their life-cycle in a similar or possibly somewhat shorter period, to which circumstance Marchiafava and Celli refer the lack of pigment.

Sporulation takes place only in the internal organs, and an infection must be especially severe before the sporulation forms appear in the peripheral blood. Marchiafava and Celli report one case of

DESCRIPTION OF PLATE VII.

A, Figs. 1 to 32. Ordinary tertian parasites stained by Mannaberg's method (picric acid and hematoxylin).

B. Quinin forms.

C, Fig. 38. Capillary of the brain containing pigmented parasites of the second group (from a preparation by Prof. Celli).

Fig. 39. Capillary of the brain containing non-pigmented sporulating parasites of the second group (from a preparation by Prof. Celli).

comatose pernicious fever in which the peripheral blood also contained very numerous sporulation forms.

Plate VII, Fig. 39, shows a brain capillary packed with sporulation forms of non-pigmented parasites; Fig. 39, *b*, represents a brain capillary in cross-section, showing the infected blood-corpuscles lying along the vessel-wall in such a way as to narrow the lumen of the vessel. These preparations were taken from a case of comatose pernicious fever. I am indebted for them to the kindness of Professor Celli.

Crescents occur here the same as with the pigmented quotidian parasites. Even in these cases, therefore, we find, after the course of several days, pigmented elements, for the crescents are without exception pigmented. Still, if the patient succumbs before the crescents appear, we have then to do with a completely pigmentless malaria. Marchiafava and Celli have actually observed such cases.

Antolisei and Angelini have frequently found pigmented organisms in the spleen, brain, and bone-marrow in cases where the finger-blood showed exclusively non-pigmented parasites. It is, therefore, wrong to deny absolutely the existence of pigmented organisms from an examination of the blood from the finger, for these may be retained in the internal organs. With this restriction—no puncture of the spleen was done—I detail the anamnesis of a case of infection by non-pigmented quotidian parasites:

D. J., aged nineteen, woodcutter, states that he has suffered for eight days from a continuous fever; no chills were perceived. Intense headache, pain in the limbs, and for these eight days constipation.

August 12, 1892, 10 A. M.: Temperature, 39.5°, patient groaning under the severe prostration. Tongue dry and fissured, spleen just palpablĕ.

Blood examination: Numerous small ameboid non-pigmented organisms.

4 P. M.: Temperature, 40.2°.

Blood examination: 1. Very many non-pigmented organisms in torpid movement. Frequent double infection of the blood-corpuscles. 2. In isolated leukocytes large pigment-granules.

7 P. M.: Temperature, 39°. Received 0.33 quinin.

August 13, 5 A. M.: 0.33 quinin.

9 A. M.: Temperature, 37.6°.

Blood examination: 1. Numerous non-pigmented organisms, endowed with ameboid movement. 2. An extremely large number of "brassy corpuscles," in some of which the parasites show active ameboid movement. In no corpuscle is there any pigment, only here and there a hemoglobin granule.

10 A. M.: 0.66 quinin.

4 P. M.: Temperature, 39.2°.

Blood examination: 1. Very numerous ameboid organisms. 2. A like large number of brassy corpuscles. 3. One sphere of the crescent class.

7 P. M.: Temperature, 40.5°; 0.33 quinin.

August 14, 5 A. M.: 0.33 quinin.

9.30 A. M.: Temperature, 37.2°.

Blood examination: 1. A smaller number of ameboid non-pigmented organisms; several with hemoglobin inclusions. 2. Isolated crescents.

7 P. M.: Temperature, 39°; 0.66 quinin.

August 15: Patient complains of exhaustion and pains in the limbs; he appears completely prostrated.

9 A. M.: Temperature, 37°; 0.66 quinin.

Blood examination: 1. Isolated non-pigmented organisms. 2. Isolated crescents.

7 P. M.: Temperature, 39.3°; 0.66 quinin.

August 16, 10 A. M.: Temperature, 35.8°; profuse sweat.

Blood examination: 1. A scanty number of small organisms. 2. Isolated crescents.

After this the patient remained apyretic.

The type of fever was pure quotidian, though from the anamnesis and the commencement of the curve it was preceded by a continuous one.

The pigment perceived in the leukocytes in the first days probably originated from the crescents, for there was not the slightest pigment to be seen in all the innumerable ameboid organisms.

The Malignant Tertian Parasite.—This variety was separated from the other forms by Marchiafava and Bignami. In its morphologic evolution it is closely related to the pigmented quotidian parasite, from which it can scarcely be differentiated in many stages of its development. According to Marchiafava and Bignami, the principal differential points are the following:

1. Its cycle of development lasts forty-eight hours.
2. The pigment sometimes shows oscillatory movements, never seen in the quotidian parasites.
3. The parasite reaches a much larger size, filling at the time of sporulation one-half to two-thirds of the blood-corpuscle.
4. Even the markedly pigmented stages are actively ameboid.
5. The non-pigmented stage lasts twenty-four hours or longer. The following differences exist between it and the ordinary tertian parasite:

1. It is in all corresponding stages smaller.
2. It frequently assumes a ring form, never seen in Golgi's parasite.
3. The pigment is more scanty and only exceptionally shows movement.
4. Infected red blood-corpuscles show an inclination to shrink, while in the case of ordinary tertian, they swell.

5. The spores are smaller, and on an average not so numerous (8 to 15).

6. It forms crescents, which the other never does.

After the statement of these differences from the other forms, it is unnecessary to give a detailed description of the pernicious tertian parasite. (For the temperature-curve produced by these parasites see subsequent paragraphs.)

Examination of the blood before the paroxysm reveals pigmented forms that usually take up about half the blood-corpuscle. At the beginning of the paroxysm no parasites at all may be found, the new generation making its appearance only after the paroxysm has lasted some time. These new forms, as previously mentioned, remain unpigmented for twenty-four or even forty-eight hours, so that they may be seen eight to ten hours before the paroxysm still unchanged, or they may become so quickly pigmented that the close of the paroxysm will show pigmented organisms.

According to the discoverers, the peculiar fever-curve is due to the fact that sporulation does not occur all at once, but intermittently. As in the other small forms, sporulation takes place almost entirely in the internal organs. The crescent formation likewise shows no differences. It is worthy of mention that the two investigators have found the relapse in this case following usually the type of the initial fever, though often more pronounced.

The majority of writers (Grassi, Feletti, Thayer, Hewetson, etc.) refuse to accept the malignant tertian parasite as a separate species. I am not prepared to deny, with the absoluteness of these writers, Marchiafava and Bignami's deduction, for I have met a not inconsiderable number of patients suffering from tertian fever who showed parasites corresponding to their description.

My attention was attracted to malignant tertian fever in the summer of 1891, before Marchiafava and Bignami had yet come forward with their publication, and only the desire of studying it more accurately detained me from publishing my conclusions at the time. In the summer of 1892, after further cases, I was able to affirm the certain existence of this fever.

The following are two histories of such cases:

K. W., aged forty-two, has suffered daily for six days from prolonged violent chills, followed by fever and sweating. The paroxysms occurred at about 2 A. M., though occasionally at 8 A. M. Intense headache, pain in the limbs, anorexia, diarrhea, a subicteric discoloration of the skin, stupor, dry tongue. Spleen evidently palpable, painful.

August 22, 1891, 11 A. M.: Temperature, 41.5° (the chill occurred at about 4 A. M.).

Blood examination: Very many ameboid organisms, some very small, others somewhat larger, all non-pigmented.

4 P. M.: Temperature, 39.8°.

Blood examination: 1. Numerous very small and somewhat larger ameboid organisms, without pigment; plural infection of a blood-corpuscle frequent. 2. Very many brassy corpuscles, the parasites of which contain fine pigment. 3. One melaniferous leukocyte.

7 P. M.: Temperature, 38°. During the night, a profuse sweat.

August 23, 9 A. M.: Temperature, 36.4°.

Blood examination: 1. Very numerous small forms, filling about one-fourth of the red blood-corpuscle. They are but slightly motile. Many of them show a little pigment, which is always at the margin. 2. Very many brassy corpuscles, with parasites usually pigmented and in ring form.

About 2.45 P. M., chill.

3.30 P. M.: Temperature, 40°.

Blood examination: Numerous endoglobular organisms at rest, about one-quarter the size of the red blood-corpuscle, containing more pigment. This pigment is sometimes scattered and in motion, again concentrated at the border and at rest.

2. Isolated sporulation forms in markedly shrunken blood-corpuscles.

3. Many brassy corpuscles.

4. Numerous infected blood-corpuscles that are shrunken and decolorized (veil form).

5. Many very young, still unpigmented, actively ameboid parasites clinging to the blood-corpuscles (young generation).

5.30 P. M.: Temperature, 40.7°.

7 P. M.: Temperature, 40°.

August 24, 9 A. M.: Temperature, 38° (about 5.30 A. M., 0.66 quinin).

Blood examination: 1. Numerous ameboid organisms, either very small or of medium size, all non-pigmented.

2. One melaniferous leukocyte.

11 A. M.: Temperature, 39.2°.

4 P. M.: Temperature, 41.6°.

Blood examination: 1. Numerous ameboid organisms of moderate size, among them a few containing pigment. 2. Many brassy corpuscles.

7 P. M.: Temperature, 40.2°; 0.66 quinin; profuse night-sweat.

August 25, 5 A. M.: 0.66 quinin.

10 A. M.: Temperature, 36.5°.

Blood examination: 1. Numerous small, marginal parasites, usually immotile, all non-pigmented.

2. One melaniferous leukocyte.

3. One sygygy (of two moderately large forms).

4 P. M.: Temperature, 37.1°.

Blood examination: The same as before; all parasites without pigment.

7 P. M.: Temperature, 37.5°.

August 26, 9 A. M.: Temperature, 37.5°.

Blood examination: 1. Isolated non-pigmented small organisms.

2. Many heavily laden melaniferous leukocytes.

3. Several crescents and spheres of the same order.

After this the patient remained apyretic and he departed before the occurrence of the relapse.

The temperature-curve (Fig. 33), containing but one pronounced paroxysm, presents an evident tertian type, in that between the two short periods of apyrexia there are pretty exactly forty-eight hours. Moreover, the fever paroxysm shows the features described as typical by Marchiafava and Bignami. The pseudocritical descent and the precritical elevation are pronounced.

Previous to the paroxysm motionless pigmented organisms were found filling the greater part of the red blood-corpuscles, which were not enlarged, but rather shrunken. During the paroxysm, and especially after it, the young, non-pigmented forms predominated.

Crescents were seen for the first time on the tenth day of the disease, after conjugation forms had been observed the day before.

A., aged twenty-seven, has suffered six days, at irregular times, from chills and fever; he complains of intense headache and pain in the limbs.

August 19, 1892, 4 P. M.: Temperature, 36°; the spleen evidently palpable.

Blood examination: Quite isolated small forms with very fine pigment.

August 20, 9 A. M.: Temperature, 38°.

Blood examination: Isolated small forms, a few containing one pigment clump.

4 P. M.: Temperature, 41°.

Blood examination: 1. Very numerous ameboid non-pigmented organisms. 2. Isolated ones containing a small clump of pigment. Plural infection frequent. 3. One crescent, which changes somewhat its form and shows an evident double contour. The pigment in it is scattered and variable in arrangement.

August 21, 9 A. M.: Temperature, 36.2°.

Blood examination: 1. Pretty numerous non-pigmented ameboid forms. 2. Isolated organisms, filling about half the blood-corpuscle and containing pigment-granules which oscillate actively.

5 P. M.: Temperature, 36.3°.

August 22, 10 A. M.: Temperature, 38.5°.

Blood examination: A very few small forms without pigment.

4 P. M.: Temperature, 39.6°.

7 P. M.: Temperature, 40.2°.

August 23: No paroxysm. Likewise none subsequently.

In this case also the temperature-curve (Fig. 34) manifests a tertian type. Moreover, it resembles more the ordinary tertian, since it shows no prolongation of the paroxysm, and a day of complete apyrexia.

The existence of a tertian fever with exclusively small, crescent-forming parasites and without Golgi's forms is, therefore, an established fact.

Yet there is still another question, namely, are the parasites found here to be considered a different species from the pigmented quotidian parasites or not? A positive answer to this question cannot at present be given, and we must await the results of further investigation. In stained preparations we find that the structure of the pernicious tertian parasite is similar to that of the other species.

In concluding our remarks on the crescent-forming species we wish to detail three histories showing that fever may occur when crescents alone are apparently present:

M., suffering for fourteen days from tertian paroxysms, which begin at about 2 P. M. with a mild chill, and soon after go over into intense fever; the last paroxysm two days ago.

August 18, 1892, 11 A. M.: Temperature, 37.2°.
Blood examination: A very few small ameboid organisms.
2 P. M.: Mild chill.
5 P. M.: Temperature, 39.6°.
August 19, 10 A. M.: Temperature, 36.2°.
Blood examination: One ameboid organism discovered after a long search.
5 P. M.: Temperature, 37.2°.
August 20, 9 A. M.: Temperature, 37.4°.
Blood examination: The same as before.
6 P. M.: Temperature, 38°.
August 21, 9 A. M.: Temperature, 36.6°.
Blood examination: Isolated crescents.
5 P. M.: Temperature, 37.1°.
8 P. M.: Temperature, 37.7°.
August 22, 10 A. M.: Temperature, 37.1°.
Blood examination: 1. Several crescents with scattered pigment. 2. Isolated melaniferous leukocytes; no small ameboid organisms.
5 P. M.: Temperature, 38°.
Blood examination: A few crescents; no ameboid organisms.
7 P. M.: Temperature, 39.9°.
August 23, 10 A. M.: Temperature, 36.3°.
6 P. M.: Temperature, 37°.
Blood examination: The same.
August 24, 10 A. M.: Temperature, 37.7°.
4 P. M.: Temperature, 37.8°.
Blood examination: Isolated spheres of the crescent order.
7 P. M.: Temperature, 40.3°.
August 25, 10 A. M.: Temperature, 36.5°.
Blood examination: Several crescents and spheres.

In this case ameboid organisms were to be seen only on the first two days, and then in exceedingly small numbers, while later crescents alone appeared. The fever was preëminently of tertian type. (See Fig. 35.)

G. C., wharfsman, suffering for three weeks from a fever that showed at first a tertian, later a quotidian, type. The paroxysms consist sometimes of chills, sometimes of fever; profuse night-sweats. Patient feels exhausted and complains of pain throughout the body, especially in the head and in the bones. Moderately pale, spleen evidently palpable.

October 7, 1891, 4 P. M.: Temperature, 38.7°.

Blood examination: 1. Very many crescents and spheres of the same order. 2. A few melaniferous leukocytes.

October 8, 9 A. M.: Temperature, 38.2°.

Blood examination: The same as yesterday, only somewhat fewer parasites; no small organisms. Hemoglobin, 70 per cent.; number of blood-corpuscles, 3,217,000.

4 P. M.: Temperature, 38.3°.

October 10, 9 A. M.: Temperature, 36.2°.

4 P. M.: Temperature, 36.5°.

Blood examination: Numerous crescents and spheres of the same order, the latter frequently showing flagella, etc.

In this case, therefore, no ameboid forms were seen, only numerous crescents and their spheres. Of the latter, a very large number were flagellated.

K. has suffered every evening for two weeks from fever without a preceding chill. Violent headache, profuse sweats. Quite anemic; spleen enlarged to percussion, but not evidently palpable.

October 8, 1891, 4 P. M.: Temperature, 37.5°.

Blood examination: Numerous crescents and their spheres; no small organisms.

October 9, 10 A. M.: Temperature, 38.5°.

Blood examination: Very many crescents and their spheres, the latter frequently with flagella.

3 P. M.: Temperature, 38.3°. Hemoglobin, 60 per cent.; number of blood-corpuscles, 2,988,000.

Blood examination: The same; a strikingly large number of spheres with flagella. In the evening, 0.66 quinin.

October 10, 9 A. M.: Temperature, 35.8°.

5 P. M.: Temperature, 37°.

Blood examination: The same; still many flagellated spheres.

October 11, 9 A. M.: Temperature, 36°.

Blood examination: The same.

5 P. M.: Temperature, 36.2°.

October 12: The patient remained apyretic, though crescents and their spheres are still to be seen in lessened numbers in the blood.

In this case, too, the ameboid organisms were entirely wanting, while flagellate spheres of crescents, as well as crescents themselves, were present in large numbers. We wish to detail here finally a case of larval malaria.

A. E., aged fifty-one, has suffered for fourteen days from typical tertian. The paroxysm occurred each time in the afternoon. The last paroxysm was yesterday. The patient is pale and cachectic looking; the spleen is evidently palpable.

September 25, 1891, 10 A. M.: Temperature, 36.2°.

Blood examination: Numerous crescents and their spheres.

4 P. M.: Temperature, 36.5°.

September 26, 9 A. M.: Temperature, 36.3°.

In the afternoon, about 2 o'clock, the patient was seized with an intense frontal headache on the right side, accompanied by prostration and chilly sensations.

3 P. M.: Temperature, 36.7°. Feverish feeling, with sweating.

Blood examination: Isolated crescents.

September 28: Yesterday apyretic and felt entirely well.

9 A. M.: Temperature, 36.5°.

Blood examination: Unchanged. Hemoglobin, 60 per cent.; number of blood-corpuscles, 3,281,000.

2 P. M.: Attack of frontal headache similar to the day before yesterday.

3 P. M.: Temperature, 36.5°.

In the same way every second afternoon subsequently there was a paroxysm of frontal headache during which the supra-orbital nerve was very sensitive to pressure. An elevation of temperature was never found.

Mixed Infection.—In the previous sections it was repeatedly shown that not only several generations of one species of parasite might be present simultaneously, but even several different species. Combinations of any of the five species may seemingly take place, though the most frequent is that of the tertian parasite, with the different forms of the second group.

These combinations may sometimes be very complicated; for instance, Golgi once found in the blood of a man suffering from remittent fever three generations of quartan parasites and two of tertian. The elevations of temperature corresponded exactly with the outline that would be theoretically constructed for such a case.

The fever type in mixed infections is sometimes manifested by a coalescence of the different components, so that frequently continued, subcontinued, or even irregular types are seen, though sometimes, too, one generation so predominates as to make the fever simple. The following are examples of mixed infection:

W. G., aged forty-three, states that he has suffered for three weeks from fever paroxysms. In the beginning these occurred daily, later irregularly, and at present every two or three days. The paroxysms show the classic features. The last occurred yesterday evening.

October 4, 1891: Infirm-looking, anemic, and cachectic man. The spleen extends beyond the border of the ribs, about three fingerbreadths.

9 A. M.: Temperature, 37.7°.

Blood examination: 1. Innumerable non-pigmented small parasites of signet-ring form, and somewhat larger, round, ameboid parasites.

2. Isolated crescents. 3. Numerous brassy corpuscles (quotidian parasites). 4. Isolated large pigmented parasites, filling almost entirely the blood-corpuscle; the pigment in them shows but little movement, and the infected blood-corpuscles are frequently hypertrophic and decolorized (fully developed tertian forms).

5 P. M.: Temperature, 38.5°. Patient feels exhausted and complains of constriction in the region of the spleen.

Blood examination: 1. Isolated crescents. 2. Isolated melaniferous leukocytes. Hemoglobin, 42 per cent.; number of red blood-corpuscles, 2,217,000. Patient receives since yesterday morning 1.0 quinin daily in three doses.

4 P. M.: Temperature, 38.4°.

October 6: Profuse night-sweats.

10 A. M.: Temperature, 36°.

Blood examination: 1. Isolated crescents. 2. Numerous leukocytes with large pigment-granules.

4 P. M.: Temperature, 36.4°.

October 16: Since the last note he has remained apyretic. Hemoglobin, 65 per cent.; number of red blood-corpuscles, 3,087,000.

The infection consisted, therefore, of crescents, quotidian and one generation of ordinary tertian parasites. The two latter yielded to the quinin, leaving only the crescents. The type of fever was quotidian, though for two days there was no absolute apyrexia, since the morning temperature of 37.5° and 37.7° indicated, in the cachectic patient, fever-temperatures.

F., aged twenty-nine, states that he has had a paroxysm in the afternoon daily for eight days. This consisted of a mild chill, several hours of fever, and slight sweating. Excruciating headache.

September 24, 1891: A tawny, subicteric discoloration of the skin. The spleen extends two fingerbreadths beyond the border of the ribs.

5.30 P. M.: Temperature, 38.7°.

Blood examination: 1. Numerous actively motile, small ameboid organisms, with very fine pigment-granules, many of them showing the signet-ring form. 2. Moderately large, pigmented, actively motile, endoglobular organisms. 3. Isolated, quite large sporulation forms containing many spores within hypertrophic and decolorized blood-corpuscles.

7 P. M.: Temperature, 41.2°.

September 25, 11 A. M.: Temperature, 36°; profuse night-sweat.

Blood examination: The same as yesterday, only no sporulation forms, yet large, endoglobular, fully developed forms.

4 P. M.: Temperature, 40.5°; in the evening, 0.66 quinin.

September 26, 9 A. M.: Temperature, 36°; 0.66 quinin.

Blood examination: A very few pigmented and non-pigmented forms.

4 P. M.: Temperature, 38.2°.

Blood examination negative.

September 30: Since the twenty-sixth the patient has been apyretic, although he sweats considerably and has become pale.

Blood examination: Numerous crescents and their spheres. Hemoglobin, 53 per cent.; number of blood-corpuscles, 3,066,000.

October 6: Still apyretic. Blood examination negative.

TABLE III.—GENERAL SUMMARY OF THE CHARACTERISTICS OF THE DIFFERENT SPECIES OF PARASITES.

	Time of Development.	Motility.	Pigment.	Maximum Size.	Form of Sporulation.	Number of Spores.	Crescents.	Change in the Infected Blood-corpuscles.
1. Quartan parasite.	72 hours.	Slight motility.	Large granules slightly or not at all motile.	Size of the red blood-corpuscle.	Daisy shapes, individual spores oval, with evident nucleolus.	6 to 12.	—	Scarcely ever decolorized; usually darker in color. Normal in size or shrunken.
2. Ordinary tertian parasite.	48 hours or less (in the anticipating type).	Active ameboid motility in the young and likewise the middle-aged forms.	Finer granules in active movement in the younger forms, though often, too, in the large forms.	Size of the red blood-corpuscle, sometimes larger.	Sunflower or grape-cluster form; individual spores small, round; nucleolus seldom visible.*	15 to 20 (often less).	—	Frequently hypertrophic. Decolorize rapidly and almost completely.
3. Pigmented quotidian parasite.	24 hours.	The non-pigmented young forms very actively ameboid; after the deposition of pigment, but slight motility.	Very fine; concentrates itself in one or two clumps. No movement.	One-fourth to one-third the size of the red blood-corpuscle.	Irregular masses.	6 to 8 (sometimes more).	+	Frequently shrink when they are either darker (old brass) or completely decolorized (veil).
4. Non-pigmented quotidian parasite.	24 hours or less.	Very active ameboid motility.	None.	One-fifth to one-fourth the size of the red blood-corpuscle.	Star form or irregular masses.	6 to 8.	+	Frequently shrink and become darker.
5. Malignant tertian parasite.	48 hours.	Active motility seen also in the pigmented forms.	Moderately fine; shows frequently oscillatory movements.	One-half to two-thirds the size of the red blood-corpuscle.	Irregular masses.	10 to 12; less frequently, 15 or 16.	+	Frequently shrink, become darker, or may be decolorized.

* In the unstained condition. When stained, it is always visible.

The infection consisted in this case of two generations of common tertian parasites and of pigmented quotidian parasites. The fever was quotidian in character.

DIAGNOSIS OF MALARIAL PARASITES.—DIAGNOSTIC VALUE OF POSITIVE AND NEGATIVE FINDINGS.

It may possibly appear superfluous, after our complete description of all the forms and phases of malarial parasites, to speak again of their diagnosis, yet our excuse lies in the fact that it is not at all rare, even at this late date, for objects in the blood to be regarded as malarial parasites which are not, and for the actual parasites to escape the observation of the inexperienced investigator.

Malarial parasites can naturally be confused only with those bodies which occur in human blood. These bodies are red blood-corpuscles, white blood-corpuscles, blood-platelets, and products of coagulation.

There is absolutely no excuse for mistaking a normal red blood-corpuscle for a parasite, and scarcely more a shadow-corpuscle, since there is not the slightest resemblance between them. Still, a thornapple-form red blood-corpuscle may be mistaken for a brassy corpuscle, or oscillating fragments of red blood-corpuscles occurring in the form of small balls, hyaline filaments, or long threads with sinuous movements may be confused with flagella. The greatest danger for the inexperienced, however, lies in the confounding of the "vacuoles" of the red blood-corpuscles with non-pigmented young parasites.

The thornapple forms are differentiated from the brassy corpuscles in that they contain no parasites. In the latter the parasites are always seen as small rings, or as hyaline, round or oval, slightly or not at all pigmented spots. Moreover, the thornapple forms are covered with sharp teeth, while the brassy corpuscles have a rumpled appearance (Plate VI, Fig. 20).

The salutatory fragments of red blood-corpuscles are always more or less the color of hemoglobin, while the oscillating flagella are entirely colorless and show sometimes one or several very fine pigment-granules. The spheric fragments and hyaline strings are, on account of their large form, scarcely similar to flagella.

The "vacuoles" of the red blood-corpuscles are in some ways very similar to the young, non-pigmented parasites. As is well known, these vacuoles are the result of mechanical injury to the preparation, and the more carefully the drop is spread out, etc., the less frequently are they seen. Vacuoles also appear when a drop of immersion oil touches the object, and after the preparation has become several hours old.

These "vacuoles" are not what their name describes them to be. They are not holes in the blood-corpuscle, but are places from which the hemoglobin has retracted, perhaps in a zoöidal way, so that only the delicate, colorless stroma remains, looking like a clear spot or small ring. The "vacuoles" have the faculty of changing their form, so as more or less to simulate the ameboid movements of parasites.

Plate IV, Fig. D, shows a "vacuole" in the act of changing its shape. This is seen on the warm stage quite frequently.

The form and size of the "vacuoles" vary greatly, from the smallest point to large figures, taking up two-thirds of the blood-corpuscle. Moreover, it is not rare to see in one blood-corpuscle many punctate vacuoles.

The most important difference between "vacuoles" and parasites is that the former show no structure, while, as living organisms, this is a characteristic of the latter.

In the unstained preparations "vacuoles " are differentiated from parasites by their markedly sharp contour; the ameboid organisms before they come to rest show an extremely delicate border, which shades off into the substance of the blood-corpuscle. The "vacuoles" further show a luster not seen in the parasites. It is difficult to express in words the details of the differentiation, yet but little experience is necessary to make it very evident in the great majority of cases.

We may add that when the ring form predominates, it speaks for parasites, but when large areas of spotted red blood-corpuscles are seen, while other parts of the preparation show none at all, the diagnosis of "vacuoles," caused probably by some local injury to the preparation (pressure, oil), is certain. It is naturally never possible to confuse "vacuoles" with pigmented parasites, since the former never contain pigment.

Among the white blood-corpuscles the only ones that can be confused with parasites are the melaniferous leukocytes so common to malarial blood. The differentiation here lies in the fact that in the white blood-corpuscles there are always one or several large, compact nuclei to be seen. In unstained preparation the parasites may occasionally show a nucleus, yet this is always vesicular and contains a dark round spot—the nucleolus.

The ameboid movement of the leukocytes should never give rise to error, because the adult parasites—the only ones that might manifest a similarity—are immotile.

Leukocytes devoid of pigment show no resemblance to parasites, if for no other reason than because parasites of this size are invariably pigmented, omitting entirely the previously mentioned difference in relation to the nuclei. It is impossible to understand how Laurie could confuse leukocytes with parasites, and this even in our day.

The blood-platelets, when isolated and round, may be confused with free spores; when they lie together in heaps, as occurs so frequently, they may be confused with sporulation forms.

In regard to the isolated blood-platelets, it should be made a rule never to diagnosticate a free spore in an unstained preparation. This diagnosis is, in the great majority of cases, impossible, for free spores possess absolutely nothing by which they can be characterized, except those of the quartan parasite, which are recognized by their nucleolus. In addition, a free spore may be confused with a large coccus or an yeast-cell in the same way as with a round blood-platelet.

It is, therefore, clear that the bodies found free in the plasma are, so far as diagnosis is concerned, best left out of consideration. In the case of stained preparations the matter is different. Here we may differentiate a blood-platelet from a spore with certainty (Plate VII, Figs. 1 and 2; 27–29) by the former staining diffusely and showing no structure.

Groups of blood-platelets are differentiated from sporulation forms by the fact that they show no pigment, while no sporulation form, with one single exception, occurs without pigment; and this exception, namely, the sporulation form of the non-pigmented quotidian parasite, is not likely to be confused, because it lies within a red blood-corpuscle; moreover, these sporulation forms scarcely ever occur in the peripheral blood.

In stained preparations the differential characteristics which we have already described in relation to the isolated blood-platelets obtain also for the groups.

Among the coagulation products of the blood only the rather uncommon accumulations come into consideration. These appear amorphous, shapeless, and lie free in the plasma. They are, therefore, harmless so far as a confusion with parasites is concerned. Besides these blood constituents, we must keep in mind foreign bodies, like epithelium, dust, and dirt particles, that in spite of the utmost care and cleanliness find their way into the preparation.

When seeking after pigment we frequently find indefinite small particles that may be confusing. Now, though malarial pigment is sometimes seen free in the plasma, especially at the time of sporulation before the phagocytes have been able to remove it, too much confidence should not be placed in such pictures, and from them alone a diagnosis should never be made.

It is of much more significance when, in unstained preparations, the pigment is found in leukocytes, even though there are only a few granules. Here they become an important diagnostic aid, especially when there is no suspicion of recurrent fever, for in this disease, too, pigment may occur in the blood.*

After recovery the pigment remains visible in the circulating blood only a very short time, being quickly deposited by the leukocytes in the well-known deposit places. In fevers of the first group no melaniferous leukocytes are seen two or three days after the last fever paroxysm; in the case of fevers produced by crescents it is different, melaniferous leukocytes being encountered as long as the crescents are in the blood.

Finally, we must remember the possibility that pigment may occur in the blood in poisoning with carbon bisulphid and carbonyl sulphid, as C. Schwalbe has shown. I have repeatedly made the experiments on mice by injecting them subcutaneously with a few drops, and can confirm, in their entirety, Schwalbe's assertions. In such cases the anamnesis would assist possible doubts. Moreover, the appearances in the blood of the poisoned animals are very different from those produced by malarial parasites. It is scarcely necessary to go into details, especially since, so far as I know, these blood changes have never been observed in man.

In the blood of rabbits poisoned with dinitrobenzol, Huber has observed large numbers of vacuoles in the red blood-corpuscles. The picture in connection with this would serve as an interesting comparison with young malarial parasites.

Placed, now, in the position where we can recognize malarial parasites, the question arises, Of what use is this knowledge? The answer to this is that the presence of one single malarial parasite in the blood establishes the diagnosis of malarial infection.

I will not go into details in regard to the assertions, made a few years ago, that "similar bodies" might be found in the blood in very different infectious diseases and cachexias. They detracted at the time from the pathognomonic and etiologic dignity of Laveran's malarial parasite, but the majority of the writers later confessed that they took objects—almost always vacuoles in the red blood-corpuscles—for parasites which were evidently not parasites. From the numerous blood examinations undertaken in our day the conviction is certain that malarial parasites occur exclusively in the blood of malarial patients.

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* The assertion has also been made that pigment occurs in the blood in Addison's disease; in two such cases that I have examined I have not been able to confirm this.

Moreover, it is not alone the presence of a malarial infection in general that may be diagnosticated, but the type of fever, and often even the severity of the attack, though naturally such detailed information is possible only to those who have had considerable experience and are acquainted with all the forms of the parasites.

It was Golgi's magnificent work in differentiating the various forms that brought this knowledge to a realization, and since that time his observations have been repeatedly confirmed. I can only add similar confirmation, in that, following in Golgi's footsteps, I have been able clearly to analyze many cases from the blood examinations alone.

The few contradictions that arose against Golgi's statements came from observers not in a position to pass a critical judgment on account of the small amount of material at their command. Moreover, the superstructure begun by Golgi has been added to especially by the labors of Marchiafava and Bignami.

I will omit a detailed explanation of the diagnosis of the type, since it would be necessary to repeat the greater part of what has already been said in relation to the special characteristics of the different parasites. For this, therefore, we refer to the proper sections, and here we will mention only a few points which come especially into consideration.

When we have before us a positive find, we must first decide whether the parasites belong to the first group (without crescents) or to the second group (with crescents), or whether both are present in the blood. This is evident to the expert in a very short time, in that predominating large pigmented endoglobular forms draw his attention to the first group, and numerous small and slightly or not at all pigmented forms to the second group. If crescents or spheres are present, it is at once evident that we are dealing with the second group. These spheres of the second group may be differentiated with little practice from the spheric forms of the tertian and quartan parasites by their sharp, often double, contour, by the peculiar changes in the blood-corpuscles, by the frequent, wreath-like arrangement of the pigment, and by the marginal "knobs."

The two species of the first group may be differentiated by the activity of the ameboid movement, by the size and color of the infected blood-corpuscles, and, in case sporulation forms are present, by their shape, size, and the number and structure of the spores. Having recognized the species, we endeavor to find out if one or several generations are present. This is very difficult for the beginner, because he is easily confused both by the large sexual forms that have overlived the paroxysm and by slight differences between individuals of the same generation, so that he may believe all stages—in other words, innumerable generations—to be present in the blood, when, as a matter of fact, there may be only two or perhaps only one generation.

It must be remembered that we are dealing with a living organism, the phases of which show rather considerable deviations, and cannot, therefore, be reckoned according to mathematic formulas. Our conclusions, consequently, in relation to the number of generations, should be based not on isolated forms, but on large numbers in the same stage of development. These stages are reckoned, and without great difficulty, according to their approach toward sporulation (therefore, the paroxysm), from the size, the motility, and the pigmentation of the parasite. The severity of the attack is, according to Golgi, in proportion to the number of parasites.*

We proceed similarly in relation to the parasites of the second group. The determination of a mixed infection is somewhat complicated, yet in the majority of cases the difficulties are by no means insurmountable.

Let us turn, now, to a negative finding. It has happened to me, as well as to other observers (it was especially Baccelli who took up this side of the question), that parasites could not be found in spite of repeated careful blood examinations, when all the symptoms, the course of the disease, and the action of quinin pointed to malaria. These cases were rare, numbering altogether 3 among 130. In any disease a negative finding is of little significance. Moreover, in very recent malarial infections, in other words, during the first days of the disease, the parasites are sometimes missed, and this is true of even those cases experimentally produced by the injection of malarial blood.

The explanation of this is that the parasites are present in such small numbers during the first days that they are difficult to find, or that they are confined during this stage to the internal organs.

In order to arrive at a certain conclusion it is, therefore, advisable, in case the examination has proved negative, to wait for one or several paroxysms, so as to repeat the examination at especially favorable times—before the paroxysm. In these cases, too, it is possible that puncture of the spleen may be justifiable.

CULTURAL ATTEMPTS.

As numerous and different as the attempts to culture malarial parasites have been, all have resulted negatively. Moreover, not only the media used in bacteriology have been employed, but also other substances, which, *a priori*, seemed to offer the parasites the most favorable conditions, yet no medium and no method have proved successful. Coronado's statement that he succeeded in culturing malarial parasites from the air of swamps, water, etc., is not of the kind to awaken confidence.

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* In general I can confirm this rule of Golgi's, yet it must be added that the individual constitution, perhaps, too, the virulence of the parasites, may influence considerably the severity of an attack.

The most that has been done so far was the preservation of parasites for one or two days.

The attempts to keep them parasitic or capable of reproduction by introducing them into the peritoneal cavities of animals met with not much better success.

Rosenbach observed in leeches which he had applied to a fever patient tertian parasites still living after forty-eight hours; at least they showed pigment movement. Sakharoff placed the filled leeches on ice; four days later he inoculated himself with the blood of one and was attacked by a fever which showed corresponding parasites (parasites of the second group).

These experiments were repeated by Blumer, Hamburger, and Mitchell. Hamburger asserted that the parasites, which were of the second group and non-pigmented, increased somewhat in size in the body of the leech and showed pigment-formation. Mitchell found that tertian parasites were still evident in the leech after ten days, though from the beginning they manifested no ameboid movement. Crescents did not change their form. Ziemann examined the malarial blood in leeches after varying intervals, and found that the chromatin, as a rule, held its color for several days.

I repeatedly fed flies with malarial blood rich in sporulation forms or crescents. The parasites were preserved only a short time and did not increase.

At Manson's suggestion Ross had mosquitos suck blood rich in crescents. He found that a very large number of the crescents became flagellate within a few minutes. Manson, who at that time regarded flagella as spores, maintained that mosquitos constituted the hosts of the malarial parasites (as they do of the filaria) outside the human body. He contended that the mosquitos "rescue" the parasites from the human blood-vessels by sucking them out, and offer them an opportunity for further development within their body. How this view, it is true, in a different form, has eventually been established is discussed in the appendix.

TOXIN PRODUCTION OF THE HUMAN PARASITE.

That malarial parasites produce a poison was first suggested by Golgi, and since then has been assumed as probable by many investigators. So far, no one has in any way described or demonstrated this poison. Its existence is assumed only to explain some of the symptoms (as, for instance, the paroxysm) that could not be explained without it. The toxicity of the malarial urine (see another section) may be considered the only concrete factor thus far discovered that points to a malarial toxin.

I have recently endeavored to prove this question in this way: I took the blood of two patients during a paroxysm, centrifugated it, and injected subcutaneously the pure serum into healthy men. In the first case I employed 1 c.c. of serum (ordinary tertian). The temperature of the person experimented on was at the time of the injection (4 P. M.) 36.7°; at 4.30 P. M., 37°; at 6 P. M., 36°. In the second case I injected 0.7 c.c. of the clear, canary-yellow serum (likewise tertian); the temperature of the person experimented on rose within fifteen minutes from 36.5° to 37.6°.

These experiments should be continued with larger quantities of serum in order to arrive at positive results. Bignami doubts the existence of a free malarial toxin, because he found the blood of the fetus of a pregnant woman infected with malaria normal.

MODES OF INFECTION.

One of the most important questions that arose in connection with malaria was, In what manner does the human being become infected with malaria? On the correct solution of this problem depended the rational prophylaxis, and it was, therefore, reasonable that so much should have been done, especially since the discovery of the malarial parasite, with this view in mind.

The problem has now been solved; it will not be unprofitable, however, to consider the older views and to trace the steps whereby the solution has been reached. There were three hypotheses in regard to this. Not one of them is new, all coming to us from ancient times. Sometimes one obtained, again another. The three theories were: 1. The water theory. 2. The air theory. 3. The mosquito theory.

1. The Water Theory.—Numerous data have been brought forward in support of the transmission of malaria by drinking-water. Though a number of these appear at first sight rather convincing, further consideration shows that no proofs have ever been offered to show that any one became infected with malaria from drinking contaminated water. The only experiment that would prove it with certainty would be, if malaria were produced in a person in a region absolutely free from malaria by the drinking of water from a malarial region. This experiment has been done, but with negative result. Celli had several people in the Roman Hospital San Spirito drink water for several days from the Pontine marshes and the swamps about Rome, but found no malaria develop. Brancaleone repeated this experiment in Sicily, with the same negative result. Zeri had 9 persons drink, for five to twenty days, 1.5 to 3 liters of water daily (in all, 10 to 16 liters each) from a malarial region; he had 16 persons inhale the same water in an atomized condition; to 5 persons he administered it by the rectum. None of them became infected with malaria. Salomone Marino also described similar negative results. The attempts, therefore, to produce malaria by means of water have so far been in vain.

In addition, there are still other facts which make these experiments more convincing. It is often necessary for ships' crews to take water from severely infected malarial coasts, to be used for drinking in the course of the voyage. Yet malarial infection on ships is extremely rare, presupposing, naturally, that the crew has not gone on land. Boudin's much-quoted case of the ship "Argo," which left Bona in July, 1834, and on which the soldiers who drank the water taken on board at Bona were attacked by malaria, while the sailors who drank other water remained healthy, has been the occasion of much argument. This case may now be looked on as settled, for there seems no doubt that the soldiers acquired their infection before going on board.

Valuable critical evidence has been added, and an interesting and striking fact stated by Rupert Norton. This writer showed that in a large number of American forts where malaria is endemic the absolute malarial morbidity has not been altered by the conduction to them of pure water.

Laveran was himself skeptical in relation to the water theory, yet seemed unwilling to dispose of it entirely. Kelsch and Kiener follow Colin, who, after a critical study, took a stand against the water theory; Fayrer and Manson, on the contrary, defended it.

Fayrer asserted that people who drink filtered water suffer less frequently from malaria than others, but, unfortunately, gives no figures, and does not even say if this is true, *ceteris paribus*.

Manson formed his conclusion on an experiment of Ross's. The latter had an Indian native drink one or two drams of water in which mosquitos had died that had previously fed on malarial blood. The mosquitos themselves were removed before the beginning of the experiment. Eleven days later the man was attacked by fever that ceased spontaneously after a few days. Ring-form parasites of the second group were demonstrated in large numbers in the blood; there were no crescents and no relapse followed.

The experiment was later repeated on other individuals, but with negative results. The first positive experiment loses most of its value on account of being done in a malarial region, where infection in other ways could not be excluded.

Isolated facts apparently supporting the water theory have been collected by Laveran,* and for further arguments we refer the reader to his work.

2. **The Air Theory.**—The view that malarial parasites rise from the soil into the air and gain entrance into the organism by way of the respiratory tract is one of the oldest and most common. The name "malaria" shows that this conviction arose among the people themselves. But in science, popular instinct and public opinion carry no weight, and it is exactly the air theory that, after years of tranquillity, has fallen under sharp criticism and been forced into the background.

Several facts are opposed to the air theory which cannot be explained by it, at least in a satisfactory way.

It is, first, very striking that severely infected and almost immune places may lie in close connection with one another; that in the same city the inhabitants of one quarter may suffer from malaria and those of another not; that in the same house, rooms looking in a certain direction may be dangerous, and others not; and that an elevation of a few meters above a severely infected swampy soil is sufficient to protect from infection. Examples of this kind are very numerous. So, for instance, it is known that crews of ships lying anchored on severely infected coasts (presupposing, of course, that they do not go on land, and that the distance from the shore is not entirely too small) are seldom attacked by the disease. Pringle mentions that the forces remaining on the English squadron anchored near the island of Walcheren were spared, while those on land suffered severely from malaria. In the Madagascar campaign (1895) the ships anchored scarcely 300 meters from the pestilential shores, yet the crews remained healthy. At Rome, outside the Porta del Popolo, malaria rages; a few hundred meters from there, the Corso is not at all dangerous. The hospital San Michele a Ripa Grande is immune; a short distance from it toward San Paolo there are severe malaria foci. The inhabitants of Paolo assert that in certain houses the rooms looking toward the sea are secure, while those looking toward the country are scourges (quoted after Bignami). Similar observations are made in great numbers from all malarial regions. In Vienna we recognize that fever occurs only about the bank of the Danube (Prater, the Danube meadows, etc.).

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* "Traité du Paludisme," 1898.

If the malarial virus was suspended in the air, it would be impossible to understand why it would not be carried by the wind, so as to display its effect at a distance from its breeding-place. Yet we could not, at this period, say that such transferences through the air had not taken place.

It was observed in many regions that the malarial cases increase when the wind blows from the direction of certain swamps. The idea that the malarial virus might be disseminated by the wind was first expressed by Lancisi, though the example that he chose to prove it was not very appropriate. Lancisi was of the opinion that the Roman Campagna was infected by the clearing of the forests under Gregory XIII, which opened up a path for the winds blowing over the Campagna from the Pontine marshes. He suggested that woods formed a sort of filter for the infected air. But Lancisi overlooked several points—for instance, on the way from the marshes toward Rome there are several places (Velletri, Genzano, Ariccia, Albano, etc.) which are entirely free from malaria, although they should come in contact with those winds sooner than the more northerly parts of the Campagna. Lancisi was correct in so far as there were numerous examples which apparently supported his idea. From recent times we may mention the observations of Jilek in regard to Pola. Jilek found that besides the amount of rain and the heat, there were other factors governing the malarial mortality in Pola, namely, the winds, and that the east and southeast winds were the dangerous ones. In connection with this we must add that the two swamps, Prato Grande and Piccolo, lie in the southwestern part of the city.

Nielly observed malaria break out simultaneously in 27 men on board the "Recherche" forty-eight hours after the ship had lain at anchor for one night in the Roads of Sainte Marie Bathurst. None of the infected had had fever previously.

Daville reports from the New Hebrides that as long as southeast breezes blow malaria is not seen, while with the appearance of southwest or western breezes it takes on the character of an epidemic. Maurel writes in relation to French Guiana: "As long as the air is still or the wind blows from a salubrious region it is possible to live within a few kilometers of a swamp without danger. Cayenne is an example of this. Yet when the wind turns and sweeps over the swamps for a few days, the places previously free begin to show numerous cases."

In almost all malarial places *ceteris paribus* endemicity apparently stood in relation to the dominating winds. Still it might have been objected that this connection was not due alone to a transference of the virus by the wind, but was dependent, too, on changes of temperature and moisture brought about by different winds. It appeared to be certain that the wind may be the medium of transference of malaria, though the distance to which this is possible is at most slight.

On this question Hirsch expresses himself as follows*: "To measure the distance in figures to which malaria may be carried by the moving air is scarcely possible, yet it is highly probable that this is short. At least all the observations that have been made on dry land would so indicate, and even more decisively, the observations in relation to the spread of the disease from the land to ships. All experience in this regard goes to show that the crews of ships lying closely enough to the coast to be surely affected by the land breezes almost always remain free from the disease as long as they keep away from the infected land itself. And this is true of the severest malarial foci."

It was, therefore, very difficult to understand why, if the virus were in the air, it would not be carried great distances. How far mineral and vegetable impurities may be conveyed was well known. Bignami, to whom we are indebted for a thorough study of this question, added another embarrassment by pointing out that infections occur most frequently when the ground is moist, not when it is dry and dusty. A further fact, difficult of explanation by the air theory, was that the hours after sunset and before sunrise are the most dangerous, and that sleeping on a malarial soil is almost as sure as inoculation.

The wide-spread opinion as to the presence of the malarial virus in the air brought with it the idea of investigating the air of malarial regions for microbes. Lancisi began these investigations, and among others we may mention Hammond, Lemaire, Maurel, Vogl, Grassi, and Calandruccio. The majority of these worked with Bouchet's aëroscope and Lemaire's condensator.

Vogl "found the air of Pola remarkably contaminated, and especially rich in certain organisms which probably stand in a genetic relation to the malaria occurring there" (quoted from Jilek). Maurel found in malarial air amebæ which he failed to find in the air of healthy places. He likewise found amebæ in the nasal mucus, a direct proof that protozoa may be introduced with respiration. Similar observations were made by Grassi and Calandruccio. These investigators found amebic cysts in the nasal mucus of doves which they had exposed for several nights to the emanations of swamps or malarial earth. Moreover, they succeeded, even though seldom, in demonstrating amebæ in dew. I tried similar experiments with the earth of malarial regions and convinced myself of the presence of innumerable amebæ in the water of condensation. These observations and experiments are now mainly, if not entirely, of historic interest only.

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* *Loc. cit.*, p. 208.

3. **The Mosquito Theory.**—Lancisi was the first to express the opinion that the insects living in the swamps, especially the mosquitos, might, by their sting, be the agents of transference of the baneful swamp virus to man.* This theory was also taken up by Laveran as the most probable one, and a number of authoritative writers, like Manson, Bignami, and R. Koch, then followed him. Manson, supported by the previously mentioned experiment of Ross, presented the matter in this way: The mosquitos suck the blood of malarial patients, thereby taking up the parasites. They transfer the parasites in some changed form to their young, which are later deposited in the external world, especially in water. This last, therefore (in the way of drinking), should be regarded as the only carrier of infection. It is the same process that Manson determined for the filaria.

Laveran, like Lancisi, expresses the opinion that mosquitos may inoculate the malarial virus into man. The manner in which this is done he does not indicate. Bignami also believed that mosquitos inoculate, by means of the proboscis, malarial parasites, which they have taken from the ground, and to demonstrate this he made several valuable experiments. He showed first, in connection with Bastianelli, that is was possible to produce infection by means of minimum quantities of malarial blood infected subcutaneously. In order to imitate the sting of a mosquito he introduced under the skin the needle of a Pravaz syringe moistened with malarial blood. In several cases this was sufficient to produce a severe malaria.

Bignami then instituted, in association with Dionisi, a series of direct experiments with mosquitos, though these resulted negatively. They collected, for instance, from a malarial focus, a large number of mosquitos ("zanzare"), brought them to Rome, placed them in a room of the San Spirito Hospital, and allowed a robust man who offered himself for the experiment to sleep there. The man remained unaffected, as likewise another individual on whom the experiment was done. Moreover, the microscopic examination of numerous mosquitos by Bignami was without result.

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* Yet Lancisi, as mentioned in another place, also suggested the other means of infection as possible.

R. Koch was of the opinion that the mosquitos suck the blood of malarial patients and transfer the parasites to their brood, and that only this generation, or possibly the subsequent one, can produce malaria by stinging. So far as his communications extend Koch seems to have made no personal experiments.

There were many observations and facts which supported this view of a connection between mosquitos and malaria. First, it is well known that the majority of malarial places are rich in such insects, though this was apparently not true in every single case. Duggan argues against Manson that there are in Sierra Leone but few mosquitos (an observation that we now know to be quite false), in spite of the fact that it is a severe malarial region. Ziemann mentions the same of Kamerun.

Anderson proposes against the mosquito theory that the mosquitos usually sting the new arrivals, while it is the old residents who usually suffer the most severely from fever. That there are many places in the world swarming with mosquitos without malaria manifesting itself is a fact, yet not one militating against the mosquito theory, since the mosquitos are only the carriers of the virus.

Laveran further insisted that the same regulations which bring about the improvement of malarial foci cause a retrenchment or disappearance of the mosquitos. The facts most readily explained by the mosquito theory were:

That malaria should not be carried by the wind, or at most but short distances, since it is well known that these insects do not leave their mother soil. The wind scarcely begins to blow before they conceal themselves under leaves, in grass, etc. It is likewise well known that mosquitos are least annoying in a room through which there is a good draft; that sleeping on a malarial soil is so particularly dangerous since the sleeping person would be a great attraction for the insects; that children are attacked much more frequently by malaria than adults; that the danger is greater during the night, since mosquitos swarm by preference at night; that there is but slight extension of malaria upward. Not because the mosquitos can fly no higher than a few meters, but because they prefer the lower atmospheric layers near the ground.

Finally, that artificial malaria has so far been produced only by the inoculation of malarial blood, which would seem to show that the disease might be produced by nature in a similar way.

A further argument for the mosquito theory lies in the analogy with the other blood diseases of man and animals. It is well known that the Filaria sanguinis is conveyed by mosquitos, the tsetse-fly disease (nagana) of horses and dogs in Zululand by the tsetse-fly, and Texas fever of cattle by the tick. Moreover, it has been also conjectured that recurrent fever is conveyed by the bite of the bedbug.

While recognizing the strength of these analogies, certain differences had to be insisted on. Texas fever is transferred from animals by means of the tick. If the infected cattle gain entrance to a healthy herd, individuals of the latter will be attacked, yet this did not seem to occur with malaria. This at first seemed to be against the applicability of Manson and Koch's parallel. If the mosquitos, after sucking malarial blood, were in a condition to produce malaria, then we ought to have found the disease spread by patients coming into a mosquito-plagued region, even though it was free from malaria.

[How this as a matter of fact does occur and how infection is spread by means of particular mosquitos we shall see later.—Ed.]

In favor of the mosquito theory, isolated experiences were adduced to show that infection can be avoided in severe malarial regions by the employment of mosquito-nets. It is well known, for instance, that Emin Pasha never traveled without a mosquito-net, and to this is attributed the fact that he never suffered from malaria. Still, the experiences in this direction were too scanty to enable us at that time to draw definite conclusions.

Moreover, it had long been recognized that a fire near at hand makes it less dangerous to sleep at night on a malarial soil. This might readily be explained by the fact that the insects are killed or rendered inactive by the smoke.

The mosquito theory was then eventually experimentally taken up from many sides, and the result has been an absolute and convincing proof of its correctness.

EXPERIMENTAL INOCULATION OF MALARIA.

Gerhardt was the first to demonstrate that malaria could be transferred to a healthy person by the blood of a patient. Since then, as Table I shows, numerous experiments have confirmed this.

At the beginning it was deemed necessary to introduce the blood into a vein of the person inoculated, but it gradually became evident that subcutaneous inoculation was sufficient, even though, now and then, a case turned out negative. The amount of blood employed fluctuated between the portion of a drop (Bignami) and 4 c.c.

The blood was taken, as a rule, by means of a Pravaz syringe or cannula, from a vein at the bend of the elbow, and immediately inoculated. Bein and Sakharoff obtained the blood by allowing a blood leech to suck it. Di Mattei in one case (Table I, experiment No. 14) mixed the blood with an equal amount of distilled water and still obtained a positive result. This experiment is of particular significance, since it shows that the parasites, at least some of them (crescents ?), remain viable even after the action of water. I employed (Table I, experiment No. 25) the blood corpuscular sediment of centrifugated blood with a positive result.

As to the relation between the type of fever and the parasites in the person inoculated, and the type of fever and parasites in the person from whom the blood was taken, sufficient has already been said. Still we may add that in a number of cases the first fever paroxysm appeared on the day, in fact, even at the hour, at which it took place in the person from whom the blood was taken (presupposing naturally a continuation of the disease).

The blood employed was taken sometimes at the time of the paroxysm, again during the intervals. Von Dochmann has affirmed that he produced in a healthy person a fever, quartan in type, by the inoculation of the contents of a herpes vesicle, taken from a person suffering from quartan fever. So far a repetition of this experiment has not been done.

Some older writers were of the opinion that the sweat of malarial patients could convey the disease—in other words, that malaria was to a certain extent contagious (Meibom, Reil). In our day this view has been completely abandoned. I investigated the sweat many times without finding parasites.

Inoculations of malarial blood into animals (monkeys, rabbits, horses, foxes, dogs, cats, guinea-pigs, mice, doves, etc.) have all been negative. Moreover, there is at present no animal known which is affected by malaria in the same way as the human being. In regard to the malaria-like hematozoa of animals, we will not enter into details, but refer only to the work of Danilewsky, di Mattei, Labbé, Gaule, Kruse, Grassi and Feletti, Celli and Sanfelice.

INCUBATION.

The experience of many observers taught that malaria, unlike other infectious diseases, had no fixed period of incubation. In the very great majority of cases the incubation seems to be about six to fourteen days. Yet isolated cases have been reported in which the disease apparently broke out a few hours after exposure to the swamp miasm, and many in which the disease became manifest for the first time months or even years after removal from malarial regions. We are now in a position, however, to doubt the accuracy of these observations or to explain them satisfactorily on the basis of the mosquito malarial cycle.

The duration of the incubation can be deduced with certainty only in cases where persons visited but once and for a short time a focus of infection, as, for instance, ships' crews that went on land for a few hours and after return to the ship left the coast, or troops that camped one night in an infected region and moved away the next day.

We mention as an example Lind's ship, "Merlin." This remained six days on the coast of Senegambia. A portion of the crew was sent on land for the purpose of obtaining wood and water. Two days after the ship set out to sea those who cut the wood became ill; one day later, the others. Blaxall reports, in relation to a battleship which remained five days in the harbor of Port Louis, that two persons became ill after twelve and fourteen days respectively, another after forty-eight, and still another after one hundred and sixty days (!).

Sorel reports that on August 8, 1881, 18 men were added to the post Takitount, which lay in a perfectly salubrious district. These were set on land on August 3, near Bougie, and started toward the above-mentioned post on the sixth. On August 18, 12 fell ill with malaria; on the twenty-first another, and on the twenty-fourth, still another. The infection resulted on the road through the unhealthy region between Bougie and Takitount. The incubation was, therefore, seven to nine days.

The determination of the incubation is much more uncertain when it concerns people who live continuously in a malarial district, since such cases give no clue to the time of infection. Yet if the person attacked visited, one or two weeks before, a particularly severe malarial region, went on a hunting expedition, or something similar, it becomes probable that the infection took place at that time.

The possibility of an incubation of a few hours was questioned by many writers. As a matter of fact, we could scarcely picture to ourselves, either by the air or mosquito theory, that the organism could be attacked within a few hours by so many parasites that they would be able to cause a fever without previous multiplication, and such a multiplication takes place in the most rapidly sporulating parasites only after the course of twenty-four hours.

If we adhere to the principle that the paroxysms of fever occur only at the moment of sporulation of a generation, these cases become even more suspicious, since we can scarcely conceive that the parasites which have just gained entrance to the organism would sporulate *a tempo*.

Hertz observed in himself, a short time (one-half hour) after he had visited a swampy region, ringing in the ears, faintness, burning in the throat, nausea, chilly sensations, and a few hours later a fever paroxysm. Plehn had a similar experience in West Africa, and though he found no parasites in the blood at the time of this first paroxysm, he found one ten days later, when new paroxysms took place. It is naturally possible only by a positive blood examination to decide if incubations of such short periods actually occur.

We could likewise with difficulty picture to ourselves the very long incubations, with a duration between one month and several years. We would sooner assume, with Thayer, that the parasites, though present, for some reason never increased to such an extent as to make the symptoms of the malarial infection manifest. After the course of several weeks or months symptoms due to the latent virus appearing, they are regarded as the first effect, on account of the absence of other symptoms. These would, therefore, resemble certain cases of syphilis in which the secondary symptoms appear without the primary sore having been remarked.

The great majority of cases (incubation from six to twenty days) are most readily explained by assuming that at the time of infection a number of parasites gain entrance to the organism, and these require a period of incubation in order to multiply before they are able to produce symptoms. From this it would also follow that the number of parasites gaining entrance would have a marked influence on the duration of the incubation. Moreover, the species of parasites would play a rôle in that the quotidian parasites, as a result of daily reproduction, would increase more rapidly in numbers than the tertian parasites, and these again more rapidly than the quartan.

Yet other individual factors, too, must have an influence on the incubation, since we see people who have been exposed to the same noxious influences manifesting symptoms not only not simultaneously, but often at considerable intervals.

The duration of the incubation in experimentally produced malaria corresponds in its variations with that of the spontaneously acquired disease. Table IV shows that the incubation of these cases, omitting the ones previously treated with serum, fluctuated between three and twenty-one days.

Quartan fever shows in five cases incubation periods of from eleven to eighteen days; the average, therefore, is 13.4 days. Tertian fever shows in seven cases incubation of from six to twenty-one days; the average is, therefore, eleven days. Seven cases with parasites of the second group (ameboid, with and without crescents) show fluctuations between three and fourteen days; the average is, therefore, 6.5 days. In two cases showing crescents without (probably with small numbers of) ameboid parasites, the incubation was thirteen and fifteen days; the average being, therefore, 14.

TABLE IV.—DURATION OF THE INCUBATION IN EXPERIMENTAL MALARIA.

Quantity of the Blood Injected in Cubic Centimeters.	0.03*	0.20	0.50	0.75	1.0	1.5	2.0	3.0	4.0	5.0	Remarks.
Quartan	....	.....	18	.....	11	....	15 11	12 25* 25* 25*	....	....	* Previously treated with serum.
Tertian	....	21*	.....	.....	....	11	12** 12* 9** 9**	6	....	....	* The amount, 0.20, consisted of blood corpuscular sediment. ** The blood was taken from a leech.
Ameboid parasites of the second group, with and without crescents	6 10	4	.....	5	....	30* 6* 17*	14 3**	....	....	.... 4**	* Previously treated with serum. ** Bastianelli and Bignami reckoned only two days' incubation for these cases, in my opinion, incorrectly.
Crescents without ameboid forms	.. ..	.. ..	.....	.....	15	....	13				

We see, therefore, that the average period of incubation is longer in the quartan than in the tertian, and in the latter greater than in the estivoautumnal type, with the exception of one case, in which blood was employed containing only crescents.

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* Portion of a drop.

Bastianelli and Bignami first called attention to these proportions. From a small number of cases these writers estimated the average duration of incubation for quartan at 13, tertian 10, estivoautumnal 3 days.

Not much significance can be attributed to the amount of blood injected, since it is not the amount of blood, but the number of parasites in it, that is of importance, and we possess no means for counting these. Yet it is evident from these cases (see table) that larger quantities of blood caused a shortening in the period of incubation.

TRANSFERENCE OF MALARIA IN UTERO.

There are only a few cases which show with certainty that malaria may be transferred from an affected mother to the fetus, and it is an established fact that this transference is not only not constant, but, on the contrary, very rare.

Many older writers, like J. Frank, Stokes, Reil, and others, have insisted on the intra-uterine transference of malaria, on account of observing an enlargement of the spleen or other symptoms in new-born children whose mothers had suffered from malaria during pregnancy. In some cases it was stated that every time the mother had a fever paroxysm she felt particularly lively movements on the part of the child, which could be attributed only to the participation of the fetus in the paroxysm. Still, such cases are not to be accepted as proofs of intra-uterine transference without further investigation. Congenital tumors of the spleen are not necessarily of malarial origin: they may be the result of lues. The clinical symptoms of malaria in the new-born are by no means so typical as in adults, and the disease should not, therefore, be diagnosticated without a blood examination. A large number of the reported cases prove nothing, inasmuch as the disease first broke out several weeks or months after birth, making the pathogenesis doubtful.

A completely convincing case was reported by Duchek. This was a premature child whose mother suffered from intermittent fever during pregnancy. The child died three hours after birth. The autopsy, done by Duchek, showed: "The skin was dark in color and exhibited here and there small ecchymoses. The pleuræ were covered with small ecchymoses. A yellowish fluid was found in both pleural cavities and in the markedly distended abdominal cavity. The lower portions of the lungs were compressed; the upper, but little distended.

The liver was enlarged, and on section brownish, yellow, and smooth. The spleen was markedly enlarged, extending to 1 cm. below the umbilicus; it was 11 cm. long, 6 cm. broad, and 2 ounces in weight. Its capsule was smooth, the substance hard and friable and very dark red. The spleen and the blood of the portal vein contained considerable black pigment in the form of large, irregular flakes and granules.

A second case was observed by Bouziau. This was a new-born child, twelve days old, which showed in the blood crescentic organisms.

Less convincing cases have been reported by Bureau, Playfair, Cima, Leroux, Aubinais, Taylor, Topi, and others. In none of these was the infection proved, either by the appearance of pigment or by the finding of parasites, yet in some, for instance, that of Bureau, on account of the clinical symptoms, the diagnosis was in the highest degree probable.

Opposition to intra-uterine transference is not wanting. Burdel asserts that he never observed it. The investigations of Bignami, Bastianelli, Caccini, and Thayer are of more importance. Bignami twice had the opportunity of examining children of malarial mothers, born by abortion before they were viable. One case was a cachectic woman who suffered from fever paroxysms shortly before the abortion (third month); the other, a woman who a few hours after the abortion (sixth month) succumbed to a pernicious attack. In both cases the blood of the fetus was entirely free of pigment and parasites, although the blood of the mother in the second case contained an enormous number of them. A third case was a pregnant woman who died in a pernicious attack; here, too, the blood of the fetus contained no parasites.

Thayer's case was a negress who had been suffering for six months from quartan, and who, during a paroxysm, gave birth to an eleven months' old fetus. The blood of the latter, neither immediately subsequent to the birth nor later, showed parasites. The placenta exhibited parasites on the maternal, but none on the infant, side.

Bignami assumes that the nucleated blood-corpuscles of the fetus are not adapted to the parasites, and that, therefore, the fetus is not attacked by malaria. Moreover, it is well known that in marked anemic patients the nucleated blood-corpuscles almost never harbor parasites. Still, recalling Duchek's finding, we cannot, with Bignami, exclude entirely intra-uterine infection.

Transference of malaria from the father to the child, as asserted by Felkin, is entirely without foundation and is highly improbable. Reports of the transference of malaria through the mother's or nurse's milk (Baxa, Felkin, and others) deserve as little attention, since the affected nurslings were in some instances simultaneously exposed to the miasmatic infection, and in others there was no proof that they actually suffered from malaria.

RELATIONS OF MALARIA TO SEX, AGE, AND OCCUPATION.

Both sexes are to the same degree susceptible, though men are attacked more frequently for the reason that they are exposed more frequently to the influences which produce the disease.

Malaria spares no age; yet children are attacked much more frequently than adults. The advocates of the air theory explained this by the assumption that the closer the layer of air is to the ground, the more malarial organisms it contains and consequently children breathe in more than adults. The mosquito theorists maintained that the skin of children, as a result of its delicacy, is less resistant to the mosquito's prick, and that children defend themselves less from the insects.

There are numerous publications in relation to the frequency of malaria in children. Among others we may mention that of Borius, which asserts that the high mortality of the natives in Sénégal is to be ascribed principally to this disease in children (compare also the section Malaria in Children and Old People).

Occupation stands in the closest relation to malaria. Avocations requiring sojourn in the country, particularly in the region of swamps, marshes, and rivers, especially when connected in any way with the working of the soil, constitute the greatest contingent causes of the disease; while occupations which confine to the city or the house are much less dangerous.

The most frequent sufferers are laborers occupied with the drying-up of swamps, in building harbors, railroads, foot-roads, fortresses, and bridges, fishermen, farmers (particularly rice and tobacco farmers), woodcutters, especially in forest clearing, etc. We must not forget, too, soldiers who, during war-time, are obliged to camp in swampy regions.

The loss in colonial armies from malaria can, under circumstances, reach enormous dimensions. As an example we may recall the campaign of the French in Madagascar (1895). Reynaud's report of this expedition states that the loss from deaths—at least 72 per cent. of which were malarial cases—amounted to 32 per cent. of the whole force. These enormous figures could certainly be reached only through an incomprehensible contempt for sanitary laws and regulations on the part of the leaders. Nobody can read Reynaud's instructive book without a feeling of the deepest compassion for the sufferings of the staff. On page 354 we find: "The advance guard, with a force of 2500 men, showed in the first months 25 deaths. The mortality increased rapidly and amounted, during March, to one man daily, during April to two, during May to four, during June to eight, and at the time of the building of the earthworks, which was done by the white troops of the Second Brigade, it rose during July to twelve, at the beginning of the month of August to twenty-four, in the middle of August to thirty-four, at the end of August to forty, and during September and October to forty-five men per day."

According to Fayrer, the British army in India, consisting of 64,137 men, had, in the year 1892, a mortality from fever of 6.95 per cent.; the native army, of 2.59 per cent.; the general population, 2.81 per cent. Throughout India, during the same year, 6,980,785 people died, among them 4,621,583 of "fevers," and of the latter, according to Fayrer's estimation, two-thirds of malaria. With what caution these figures must be received we have already pointed out.

The English vessels "Monarch" and "Media" carried, in the summer of 1842, an expedition into the valley of the Xanthus (Asia Minor), in order to make excavations. Among 120 people landed from the "Monarch," 84 were attacked by malaria, and of these, 9 died. Altogether, among 153 landed, 104 were attacked, of whom 10 died and 21 were disabled (Friedel).

Moreover, not alone in the tropics, but even in temperate climes, armies suffer frightfully at times from malaria. It is only necessary to mention the expeditions from England to Holland in 1747 and 1804. On this latter expedition England sent an army of 36,481 men to the island of Walcheren. Fifty days after landing 10,000 were in the hospitals with malaria, of whom 25 to 80 were dying daily. Altogether 36,000 men were attacked—*i. e.*, almost the entire army (quoted from Maclean).

In the Russian-Turkish campaign (1877–1878) the Russian army on the Danube showed 140,000 malarial cases, with 1092 deaths. In Pola in August, 1864, before the introduction of the sanitary improvements, 27 per cent. of the local force suffered from malaria, and this amounted to 90.6 per cent. of the entire morbidity (Jilek). In the year 1880 the force in Pola consisted of 1416 men, of whom 529 were attacked by malaria (Krumpholz).

DEBILITATING CIRCUMSTANCES PREDISPOSING TO MALARIAL INFECTION.

As in other infections, so likewise in malaria, badly nourished, not properly sheltered, overworked individuals are more frequently attacked than those living under better conditions.

An outbreak of malaria has not infrequently been referred, both by lay people and by physicians, to indigestion, excesses in Baccho, violent bodily efforts, psychic emotions, colds, etc. It is scarcely necessary to say that this is a false conception, though it is true that these influences may bring about a manifestation of a latent malaria. It is an interesting and important practical fact, to which we will recur again, that a person who suffered several months before from malaria may, as a result of these factors, display a relapse.

Slight traumas of the spleen, a douche over the region of the spleen, cold baths, mountain-climbing, or the outbreak of another infection may act in the same way. Duchek has observed that in infected regions malaria not rarely follows pneumonia, typhoid fever, etc. All these cases are to be regarded as relapses. In the same category, too, I would place Griesinger's cases, in which persons who dwelt for a long time in malarial places manifested the disease for the first time after they had left these regions and gone to another healthy place. In some countries the eating of green fruit, especially melons or cucumbers, and sometimes even the drinking of milk, have been ascribed as the cause of the fever. This naturally could be true only in the previously mentioned sense.

INFLUENCE OF RACE.

All the races are susceptible to malaria, yet numerous writers (Lind, Boudin, William, and others) maintain that negroes enjoy a relative immunity.

The English Niger Expedition (1841–1842) consisted of three ships; the crews were made up of 145 whites and 158 negroes. Among the whites, 130 were attacked with fever, of whom 40 died; among the negroes, only 11 suffered, and these from mild cases, none of them dying. It is interesting to note that the 11 affected negroes came from the West Indies and had lived some time in England, while the remaining negroes were Africans, principally Kru people. This would seem to indicate that the relative immunity was not in the race, but was acquired by the negroes in the malarial regions. Moreover, this assumption is supported by the fact that the negro children in Sénégal suffer in an extraordinary way from malaria (Borius).

The garrison of Ceylon showed the following distribution of malaria among the different races. Among 1000 men of the force there occurred:

	Cases.	Deaths
Negroes	(?)	1.1
Hindus	376	4.5
Malays	337	6.7
Singalese	441	7.0
Englishmen	485	24.6

Moreover, there are regions, like Madagascar and French Guiana, occupied only by negroes, other races not being able to stand the malaria (Maurel).

In East Africa, according to Plehn and R. Koch, the negroes of the coast suffer from only mild attacks or are immune. Koch believes that the coast negroes are immune by heredity. Laveran assumes, with Darwin, that the negroes as a race have a natural immunity, and cites as proof the fact that when the disease broke out on the island of Mauritius, which was free from malaria before 1866, the negroes were spared almost to a man.

Against their assumption we offer the previously mentioned morbidity among negro children, and also the fact, observed by Plehn and Koch, that in East Africa only the coast negroes are immune, while the Mschamba negroes of the non-infected Usambara Mountains, the negroes of Dahomey, the Kru and Akra negroes, the Sudanese, in one word, the negroes of the non-infected interior, are susceptible.

Other communications question even the relative immunity of the negroes. In the United States the mortality of the negroes from malaria, in contrast to that of the whites, stands in a relation of 48.3 to 30.7 (quoted from Davidson). Pieroz found that in the West Indies the negroes suffered the same as other races from malaria.

The general impression seems to be that the Ethiopian race has the faculty, in malarial places, of acquiring a considerable immunity.

Other races seem to possess this faculty to a lesser degree, or, like the Caucasian, not at all. It has been generally observed, for instance, that Creoles manifest no immunity, but, on the contrary, suffer extremely frequently and severely.

The American race (Indians) are, according to Maurel, very susceptible, though he became acquainted with one tribe (Galibi Indians) in which he never saw malaria. The Caucasian race is susceptible in all its branches; and of this race, the Europeans are least resistant.

The Arabians are about equally susceptible, though they show pernicious cases less frequently.

According to Fayrer, the native Indians are more frequently attacked than the Europeans; in ordinary years the mortality of the Europeans from malaria amounts to 7 per cent., that of the natives, to 18 per cent. Again we must repeat our caution as to the validity of such figures as these. In India it has been the practice to consider every case of "fever" as one of malaria.

The Mongolian Race.—In Tongking malaria is wide-spread. Moraud observed that the Tongkingese are as susceptible as the Europeans; the Chinese are also very susceptible.

The Japanese seem equally predisposed. In the year 1884 the Japan army showed 36.3 per cent. of its whole force affected with malaria (de Santi).

According to Pellereau, on the island of Mauritius (Ile-de-France) the frequency of the disease descends as follows: Indians, Creoles, Europeans, Chinese. The Chinese present usually milder symptoms.

F. Plehn reports that the Chinese coolies on the Kongo and on Fernando Po Island are frequently attacked.

ACCLIMATIZATION—ACQUIRED IMMUNITY.

The majority of observers maintain that there is, especially among Europeans, no acclimatization—that is, no immunity to the fever after a long resort in fever regions. On the contrary, daily experience teaches that a person who has been once attacked shows an increased predisposition. If the fact is adduced for acclimatization that subsequent relapses become constantly weaker, the many cases in which the relapse is pernicious and fatal may be brought forward in opposition.

Kelsch and Kiener deny any acclimatization for Europeans and allow only a relative tolerance. This consists in a decrease of the symptoms after a long infection, or, in other words, a diminished reaction on the part of the organism. Yet this does not prevent, as both writers add, the average duration of life from standing below the normal, and the progressive depopulation of these regions. This is about the same thing as Laveran reports among the Arabians in Algiers. They react less to the infection and manifest less frequently grave pernicious forms, although cachexia is not uncommon.

Maurel asserts that in French Guiana he could trace no white family further than four generations, although for hundreds of years thousands have been immigrating there. He states this in support of the assumption that no immunity is acquired by the Caucasian race. It was here that Maurel made the observations mentioned before in relation to negroes being more resistant.

Koch believes in an acquired immunity, at least for non-Europeans. He writes *: "The Indians who came recently to the East African coast are exceedingly susceptible to tropical malaria; some of the worst cases that I saw were in Indians. Still, thousands of Indians may be found on the African coast who are apparently immune. The same seems to be true of the Arabs, and we have similar reports about the Chinese at Sumatra. The Chinese coolies just after immigration are very susceptible, and many die. After living some time in Sumatra they lose this susceptibility and are then more highly valued and better paid. In consideration of these facts there is no doubt in my mind that malarial immunity does exist."

In this relation I would like to say that we must distinguish between genuine immunity and what Kelsch and Kiener have designated "relative tolerance," or diminished reaction. We can characterize as immune only the individual in whose blood the parasites will not live, and not one whose blood harbors the parasites, with constant diminution of the hemoglobin, and who shows gradually progressing cachexia, even though manifesting no regular paroxysms. With Kelsch and Kiener we will designate this latter condition as "relative tolerance." This condition is very well known, even among Europeans. Many investigators, myself among them, have observed in the blood of old malaria cases considerable numbers of parasites without any manifestation of fever. Livio Vincenzi mentions a series of old malarial patients who showed quartan parasites (with sporulation forms), but no symptoms, and who would buy no more quinin. Van der Schwer reports the same with parasites of the second group, and he asks the question if this is not a species of immunity. The Arabs mentioned by Laveran, who exhibited no fever, but declined under the cachexia, probably possessed this tolerance.

If malarial parasites were like ordinary saprophytes, our distinction in regard to immunity would be of no practical importance. But this is not the case; on the contrary, their evolution is closely associated with the destruction of the red blood-corpuscle, and the distinction, therefore, becomes decidedly practical.

In our opinion the question is whether it is possible for a person

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* *Loc. cit.*, p. 311.

to become actually immune or only arrive at a stage where, without fever paroxysms and intervals of actual disease, he gradually succumbs to the cachexia. Among Europeans we believe only the latter to be possible. If it is different with other races, it must be left to the future to decide.

MALARIAL EPIDEMICS.

We occasionally see epidemics of malaria in regions where it otherwise does not exist, or exists only in a mild form. At such times the malaria cases around the endemic foci also increase in number and severity.

The causes of malaria epidemics are usually to be found in widespread inundations, by which places otherwise free become adapted for the development of the malaria-carrying mosquito. The malaria epidemic at Paris on the occasion of the construction of the boulevards is well known. In this case it was undoubtedly the overturning of the earth that provided the conditions, viz., small collections of water in which the anophelines can readily multiply and so transmit infection from the sick to the healthy. Yet there are also epidemics for which no reasons can be found. Epidemics usually limit themselves to one summer, but may recur several years after one another.

Europe was afflicted several times during the course of this century. The pandemic of 1806 spread over a large part of northern and northeastern Europe and lasted until 1812. An uncommonly large and severe pandemic, that spread almost over the whole earth, began in the year 1823 and lasted until 1827. Other epidemics occurred in the years 1845 to 1849, 1855 to 1860, 1866 to 1872 (Hirsch).

Griesinger calls attention to the fact that malaria epidemics sometimes precede cholera epidemics, and refers to the occurrence of the two diseases after one another in India. Davidson assumes a close connection between the two infections. Dysentery, too, is frequently found endemic in the same places as malaria. Such observations as these it is also possible to harmonize with our present knowledge, for the water—the breeding-place of mosquitos—is a factor which affects also the prevalence of such diseases as cholera and dysentery, but, of course, for a totally different reason.

Malaria has also been brought into relation with influenza, on account of sometimes following influenza epidemics. Hertz frequently observed malaria and typhus together, though he was unable to state anything about typhoid.

MALARIA IN ITS RELATION TO THE MOSQUITO.

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HISTORIC.

It will serve no useful purpose here to follow the acute controversies as to priority which have arisen, not only as to the discovery of the malarial parasite, but also within the last few years as to the mosquito cycle. We shall give merely the principal dates and facts in the matter. On November 6, 1880, Laveran discovered the malaria parasite in Algeria and communicated his discovery to the Academy of Medicine on November 23 and December 28, 1880. King, in 1883, advanced his theory that the malarial "poison" is conveyed from marshes and human beings by mosquitos. Laveran, in 1884, believed that mosquitos were the agents concerned in producing malarial infection. Koch, in 1883-1884, suspected the mosquito. Manson's article, in 1894, was, however, the true starting-point of mosquito-malarial work. It was based on his previous discovery that mosquitos are the intermediate hosts of Filaria bancrofti. The "flagellating bodies" which had so long puzzled observers he considered to be the forms of the parasite by which it is able to survive in water, from which, subsequently, man was infected by drinking the water containing these resisting forms, or, on drying up of the water, by inhaling them in the air. Ross was stimulated by Manson to pursue this line of investigation. In 1895 he began to investigate the fate of these flagellating bodies seen under the cover-glass, and fed patients on drinking-water in which mosquitos previously fed on malarial patients had died. In 3 out of 22 cases "a slight but noticeable reaction" occurred, and they were thought to be "in favor of the truth of Manson's theory."

Experiments were next undertaken to see if the mosquito could convey the germs from the blood of a malarial patient to a healthy one immediately after feeding,—in fact, mechanically,—but the results were negative. In 1897 Ross investigated more closely the different kinds of mosquitos in malarious regions and found three kinds: (1) Brindled (= *Stegomyia*); (2) gray (= *Culex*) and (3) dapple-winged (= *Anophelinæ*). These mosquitos, then, of all kinds, were fed on malarial patients and a search was made in the stomach and tissues for a possible developmental form of these motile filaments of the flagellating bodies—at first with no success, but later dapple-winged mosquitos were used; eight only of these were procured. They were fed on malarial patients on August 16 and the stomachs examined, and on August 20, 1897, in one of the surviving mosquitos delicate circular cells in which were a few granules of pigment were found in the stomach. The last survivor of the original batch was dissected on the following morning, five days after feeding, and again these bodies were found, and they were larger. Though the pigment was difficult to explain, as some developmental form of the motile filament was being searched for, yet they gave the clue as to what the unknown developmental form was like, and in what kind of mosquito it was to be found. In September further experiments were made, and of two dappled-winged examples reared from larvæ that had fed on crescent cases, one that was killed two days later contained a large number of these pigmented cells.

Now, in 1897, MacCallum, observing the flagellating bodies and flagella in *Halteridium* in birds, had seen the motile filament break off and penetrate the other form of cell in the blood, which, as in malaria, did not flagellate, but when the filament had penetrated it, became elongated and capable of movement. Manson was able to connect this observation with the previous one of Ross. These pigmented bodies in the stomach of the mosquito were "vermicules," or fertilized female cells. The function of the "flagella" was at last explained. In this connection Simond's views that similar flagella seen in the *Coccidiidæ* were male elements was of great importance. Ross at the time was so situated as to be unable to continue his work on human malaria, so he pursued the same line of investigation with the *Proteosoma* of birds. On March 20, 1898, out of nine mosquitos fed on *Proteosoma* of birds, five contained pigmented cells; the control mosquitos that had not fed were negative. The experiments were extended, and altogether, out of 245 gray mosquitos fed on birds with *Proteosoma*, 178, or 72 per cent., contained pigmented cells, while out of 249 fed on birds without *Proteosoma* none contained parasites. In July, 1898, the development of these bodies was followed. It was found that the cysts increased in size and that the thread-like bodies inside of them, which had been noticed in similar experiments, apparently traveled to the thorax. They were eventually found in a glandular organ, the salivary gland, and it appeared certain that they passed out with the poison secretion. This idea was put to the test, and five birds free from parasites were exposed to the bites of mosquitos that had previously fed on birds containing *Proteosoma*, and which contained the thread-like bodies in their salivary glands. Fourteen days later all these five birds contained parasites in their blood. Thus was completed the demonstration of the development of the malarial parasites in mosquitos and the mode by which they were transmitted. Though it was in birds that the complete cycle was first followed, yet it was in man that the pigmented cells had first been seen which gave the clue to the discovery. The complete cycle in man was then established by the work of the Italians. We may now briefly consider their results. Ross had "shown that not every species of mosquito can give lodgment to a given hematozoön. In fact, Ross found the developmental stages of his *Proteosoma coccidia* only in the gray mosquito" (Marchiafava and Bignami). So that it seemed likely that only a particular species of mosquito can transmit the infection to man. Grassi consequently took up the study with a view to determining the distribution of particular species of mosquitos in malarial regions, and came to the conclusion that in malarial regions there are species present which are not present elsewhere. (This, we now know, was a premature conclusion, and there are exceptions to the statement, but it had a considerable element of truth in it.) In 1898 Grassi and Bignami succeeded in producing malaria in man by the bite of mosquitos collected from malarious regions (fortunately for the success of their experiments there were a few specimens of *Anopheles maculipennis* among those used, though the majority were *Culex*), and they even attributed the result to the culices. Further, on November 28, 1898, Bastianelli, Bignami, and Grassi had succeeded in tracing out the complete development of malignant tertian parasites in *Anopheles maculipennis*. The problem was completely solved.

THE MOSQUITO-MALARIAL CYCLE.

Before considering in detail the developmental cycle of malaria parasites in certain mosquitos it will be well to review briefly their zoölogic position, for, in the first place, we shall see their relationship to other protozoan parasites, and, secondly, we shall obtain a knowledge of the terminology which is common not only to the malaria parasites, but to other allied parasites, chiefly of epithelial cells, and not of the blood-cell. We shall then, when considering the actual development in the mosquito, be in a position to use terms with a definite zoölogic meaning rather than the terms first used when experimental discovery had outrun zoölogic theory.

DIVISION.	SUBDIVISION.	CLASS.	SUBCLASS.	ORDER.	SUBORDER.
Protozoa.	Plasmodroma.	1. Rhizopoda.			
		2. Mastigophora.			
		3. Sporozoa.	1. Telosporidia.	1. Coccidiomorpha.	1. Coccidia.
					2. Hemosporidia ("malaria parasites").
				2. Gregarinida.	1. Eugregarinaria.
					2. Amebosporidia.
			2. Neosporidia.	1. Cnidosporidia.	1. Myxosporidia.
				2. Sarcosporidia.	2. Microsporidia.

The *Hemosporidia*, under which designation are included the malarial and other blood-parasites; together with the Coccidia, which are protozoan parasites of epithelial cells form two suborders of the order *Coccidiomorpha*, while the nearest allied order to this latter are the *Gregarinida*, also parasites on epithelial cells. In order to gain a further insight into the relationship of these orders it will be necessary, first, to define briefly the characteristics of the *Sporozoa* and its subdivisions, and finally of the *Hemosporidia* and the somewhat heterogeneous assembly that are classified under this heading.

Sporozoa.—They are more especially characterized by the property of sporulation, which consists in the formation, from the parent organism, of a number of minute nucleated bodies. These spores are, in the majority of cases, but not always, inclosed in a sheath and characterize the class. Further, the *Sporozoa* generally exhibit two modes of reproduction: the first serves to increase the number of parasites within the same host, causing, as it is termed, an auto-infection; whereas the second method, or that of disseminating the species, produces a new infection. It is the spores that are concerned in this latter process that we have referred to above, and though generally protected by a cyst or sheath, yet the important exception to this statement occurs in the case of the malaria parasites. The protected spores are termed chlamydospores (χλαμύς = a garment), or simply spores, while the unprotected are termed gymnospores. We should note, in passing here, the use of the word spore in a double sense, viz., (1) for the cyst and its contents, and (2) for the contents alone, but to this point we shall return in considering the cycle of a sporozoan parasite.

If we refer to the table, we find that the class *Sporozoa* is divided into two subclasses,—(1) *Telosporidia;* (2) *Neosporidia,*—based upon the following differences:

Telosporidia.—Reproduction (sporulation) follows when growth is complete.

Neosporidia.—Sporulation proceeds during the process of growth. The *Neosporidia* do not concern us here more closely; we may, therefore, follow the subdivisions of the *Telosporidia*, which are divided into two orders:

(1) *Coccidiomorpha.*—Generally intracellular, reproduction anisogamous—*i. e.*, the male and female cells concerned in the process are microscopically (differentiated) distinguishable.

(2) *Gregarinida.*—Extracellular during the larger part of their development (intracellular in youngest stages). Reproductive process generally isogamous—*i. e.*, the male and female cells indistinguishable. Finally, the *Coccidiomorpha* are divided into:

(1) *Coccidia.*—Parasitic especially on epithelial cells, never on blood-cells; they are never ameboid; the spores are inclosed in a sheath.

(2) *Hemosporidia*—including malaria parasites parasitic on blood-corpuscles. The endoglobular forms may be ameboid. The spores are naked.

These, briefly put, are the main differences between the various divisions and subdivisions of the *Sporozoæ*. Further differences and also points of similarity will become apparent when we follow out the life-history of the sporozoan parasites. In the life-history of these parasites there is, as a rule, a double cycle, the vegetative cycle, cycle of growth, or asexual cycle, and the multiplicative cycle, cycle of reproduction, or sexual cycle. The asexual cycle has also applied to it the terms schizogony, monogony, or trophic or endogenous cycle, while the sexual cycle is also called the cycle of amphigony, sporogony, or reproductive or exogenous cycle. Now, the *Gregarinidæ* differ from the *Coccidiomorphæ* by the fact that in the former the endogenous cycle is exceedingly rare, though it probably exists, whereas in the *Coccidiomorpha* we have always the two cycles, endogenous and exogenous. It will be simpler, first, to consider, therefore, the cycle in the *Gregarinidæ*.

1. The earliest stage of the gregarine is a small, nucleated body seen occupying the epithelial cell. In this stage it is sometimes called a trophozoïte, because it is being nourished by the host cell and is growing in size. It eventually becomes free, and then begins its sexual life. The sexual cells which eventually conjugate are known as *gametes*, or, as they give rise to gametes, *gametocytes*. The male is indistinguishable from the female, so the sexual process in this case is termed isogamous, in contradistinction to the anisogamous sporogony, where the male and female gametes are easily distinguished.

2. Two gametocytes (or sporonts) become associated, and, without uniting, become surrounded by an adventitious cyst.

3. Changes next occur in each gametocyte by which the cytoplasm is split up into a number of small nucleated masses or *gametes*, while a portion of the original protoplasm remains unused as a "residuum," "reliquat," or "Restkörper." These nucleated bodies, the gametes, are also termed sporoblasts.

4. Until now there has been no true conjugation; this next proceeds: each of the gametes conjugates with another, producing a *zygote* or *definitive sporoblast.*

5. The sporoblast next becomes encysted in a sheath, so that the sporocyst now contains a spore. This term is not uncommonly applied to the whole structure, and not solely to the contents.

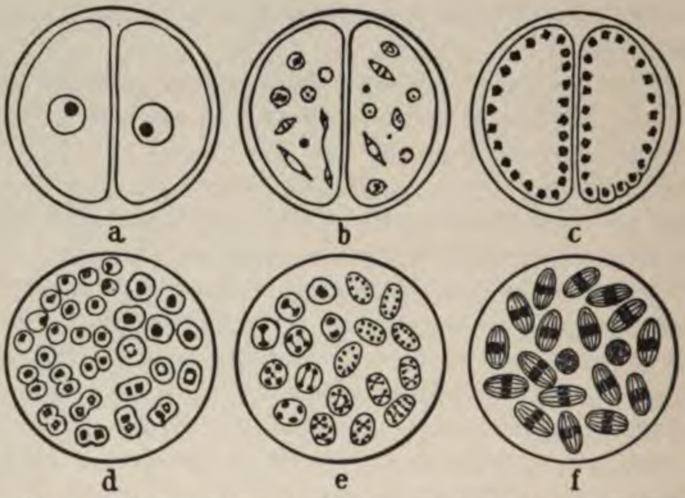

Fig. 2.—Showing Conjugation and Spore-formation in Gregarines (after Calkins and Minchin).

a, Union of two sporonts in a common cyst; b, mitotic division of the nucleus of each sporont; c, commencing formation of gametes; d, formation of sporoblasts; e, division of the nuclei of the sporoblasts; f, cyst with ripe spores, each containing eight sporozoïtes.

6. The spore, in its turn, undergoes subdivision, forming a number (eight) of spindle-shaped bodies termed *sporozoïtes;* there is here again a "residuum," in this case termed the "sporal residuum," while that of the gametocyte is termed the "cystal residuum."

7. It is these sporozoïtes which, when they are set free by the destruction of the sporocyst, give rise to an infection in a new host. They are freely motile, and can penetrate the cells of the host. The sporocysts containing sporozoïtes are, in the case of the gregarine, *Monocystis*, spindle shaped, and were originally known as *pseudonavi-*

cellæ. They may be found with great ease in the testes of the common earthworm (*Lumbricus terrestris*). This cycle may be expressed by the following notation*:

$$\left.\begin{array}{l}\text{Sporozoïte} \longrightarrow \text{trophozoïte} \longrightarrow \text{gametocyte (sporont)} \times n \text{ gametes}\\ \text{Sporozoïte} \longrightarrow \text{trophozoïte} \longrightarrow \text{gametocyte (sporont)} \times n \text{ gametes}\end{array}\right\} +$$

$$= n \text{ zygotes (sporoblasts)} \longrightarrow n \text{ spores} \times 8\, n \text{ sporozoïtes.}$$

This cycle is then a single one, viz., that of producing a new infection. It is called *monogenetic*, in contradistinction to that of other *Sporozoa* which are *digenetic*—where there are two cycles, the one producing *auto-infection*, the second, a *new infection* of a fresh host. This monogenetic cycle is one of *sporogony* or amphigony. It is the one we have just traced. The cycle of *auto-infection*, of *schizogony*, of *monogony*, the *asexual cycle*, the *endogenous cycle*, for by all these various terms it is known, we shall first discuss, and then follow out, the relationship of the two cycles to each other in a typical Coccidian. In the asexual cycle, then, a parasite divides into two or more parts by fission, or gives rise, without any complicated process similar to that we have followed above, into a number of spores, gymnospores surrounding a residuum. The parasite that gives rise to these naked spores is known as a *schizont*, in contradistinction to a sporont, and the "spores" themselves are termed *merozoïtes*, in contradistinction to *sporozoïtes*, the final stage, as we have seen, in sporogony. By medical usage, at any rate, the term spore has long been applied to the small nucleated body into which a parasite (malarial) divides in the blood, but it should be clearly understood that it is not the same as the spores of the sexual cycle.

The first stage is that of a nucleated body occupying the epithelial cell; growth proceeds; the parasite gradually destroys the cell, so that but little of it is eventually left. The mature parasite or trophozoïte proceeds to subdivide by *schizogony*, and so is termed a schizont. A number of nucleated bodies are formed—merozoïtes. Each of these, when set free from the containing residue of epithelial cell, is capable of infecting a fresh cell of the same host, and so an auto-infection is produced. The merozoïte having gained the fresh cell, gains also a new name, trophozoïte, which, in its maturity, is termed a schizont, and so the cycle is repeated until an immense infection of the host takes place, and, possibly owing to the conditions now being unfavorable, reproduction or sporogony—the sexual cycle—supervenes. This takes place in the following way: A mero-

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* $\longrightarrow$ signifies becomes: × signifies a multiplication of individuals; $\}+$ signifies conjugation and fusion of gametes.

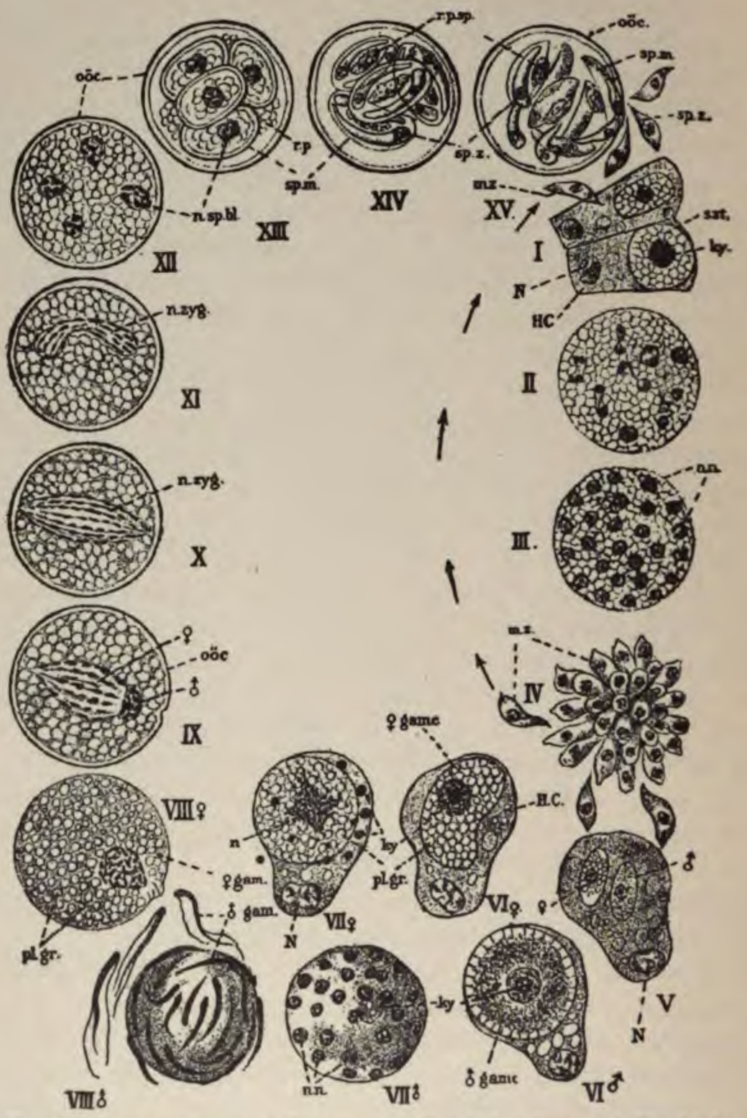

FIG. 3.—LIFE-CYCLE OF A COCCIDIAN (after Schaudinn and Minchin).

I, Epithelial cell, showing penetration of a merozoïte and its growth into a schizont; II, division of the nucleus of the schizont; III, formation of numerous daughter nuclei; IV, formation of merozoïtes; V, an epithelial cell containing a macrogametocyte (♀) and microgametocyte (♂); VI and VII (♀), stages in growth of the macrogametocyte; VI and VII (♂) stages in growth of the microgametocyte; VIII (♂), formation of microgametes (flagella); VIII (♀), mature macrogamete, emitting a cone of reception; IX, zygote or oöcyst; X, complete fusion of male and female nuclei; XI and XII, subdivision of the nucleus of the zygote; XIII, formation of sporoblasts; XIV, formation of sporocysts containing sporozoïtes; XV, escape of sporozoïtes.

zoïte (in fact, the young parasite), instead of becoming a full-grown trophozoïte—*i. e.*, a schizont—grows into two different sexual cells, termed gametocytes; the male cell is a microgametocyte and the female cell a macrogametocyte. We need not discuss here the differences between these: it will be sufficient to say that they can be readily differentiated. These give rise to microgametes and macrogametes. By this time the macrogamete and microgametes are free in the gut. The female cell, or macrogamete, attracts the male elements, or microgametes, and eventually one penetrates the female cell. The product of the union thus of a male and female cell is known as a *zygote*. Around the zygote is now secreted a sheath, which is termed the *oöcyst*. The zygote is thus a nucleated cell resulting from the fusion of male and female elements. Its nucleus now proceeds to divide, giving rise to a number of sporoblasts and a residuum. Around each sporoblast a cyst is formed, and so we have, as in the gregarine, a *sporocyst* containing a spore, or "a spore" simply. Further, the spore also subdivides, giving rise to sporozoïtes, two or more. The sporozoïtes, when set free from the sporocyst, produce the new infection of another host, and so we arrive at the first stage, where a sporozoïte is penetrating an epithelium cell. This cycle may be expressed in the following way:

$$\text{Sporozoïte} \longrightarrow \text{schizont} \times \text{merozoïtes} \longrightarrow \text{schizonts} \times \text{merozoïtes} \longrightarrow$$
$$\left.\begin{array}{l} \text{♂ gametocytes} \times n\ \text{♂ gametes} \\ \text{♀ gametocytes} \longrightarrow \text{♀ gametes} \end{array}\right\} + = \text{zygotes} \times m\ \text{spores} \times m\ n\ \text{sporozoïtes.}$$

We may now follow out finally the life-cycles of some of the *Hemosporidia*, and we shall do so in the same schematic way, leaving to a later stage a description of the details of the actual process. The *Hemosporidia* differ from the rest of the *Coccidia* in the special mode by which the new infection is conveyed. While in the *Sporozoa* generally the spores which escape from one host are usually ingested by the fresh host, in the case of the malaria parasite the new infection is transmitted through the agency of the mosquito.

In the case of the malaria parasites there are also two cycles, the asexual and the sexual, or, to give them their synonyms, that of auto-infection, schizogony, monogony, or endogenous cycle, on the one hand, and that of the new infection, sporogony, amphigony, or exogenous cycle, on the other. The stages are closely analogous to that of a Coccidian, with some slight differences:

(1) The young parasite or trophozoïte in the blood-cell grows up and becomes a schizont (sporulating body), which divides by schiz-

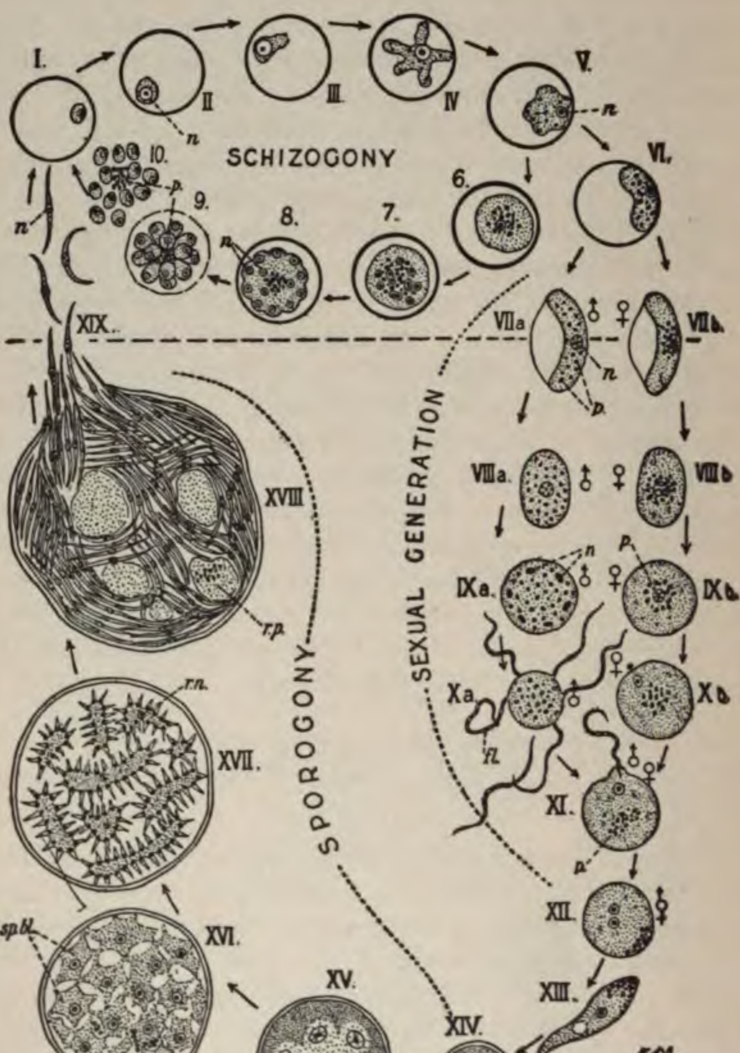

FIG. 4.—LIFE-HISTORY OF A MALARIA PARASITE—LAVERANIA MALARIÆ (after Minchin).

I–V and 6–10, Cycle of schizogony, or fever-cycle; VI, indifferent gametocyte; VII*a* male crescent; VII*b*, female crescent; X*a*, emission of microgametes (flagella) by the male; XI, fertilization of female; XII, zygote; XIII, vermicule or oökinete; XIV, oöcyst; XV and XVI, formation of sporoblasts; XVII, formation of sporozoïtes; XVIII, mature oöcyst containing numerous sporozoïtes; XIX, free sporozoites. The dotted line represents the passage from the blood to the mosquito and in the reverse direction.

ogony into a number of spores or merozoïtes. These merozoïtes arranged around the central clump of pigment constitute the "daisy" or "roset" form. They become free in the blood by disintegration of the blood-cell, and again attack other red cells, producing auto-infection, and so the asexual cycle is completed.

(2) At a certain period, however, the young parasites, merozoïtes, or sporozoïtes, instead of following this course, develop into sexual cells of two types—the microgametocyte and macrogametocyte, which can be recognized in the blood.

The next stage (in the mosquito's stomach) is the development of microgametes (or flagella) from the male cell, and the fertilization of the macrogamete. The product of the conjugation is here also termed a *zygote.* It has been also termed a *copula* and *amphiont,* and more appropriately, from its properties, a *vermicule* or *oökinete.* This becomes encysted and constitutes the *oöcyst.* Within this develop sporoblasts, and these give rise, without the intervention of any spore stage, to sporozoïtes ("sickle-bodies"). These eventually leave the mosquito during the act of "biting" and infect the fresh blood-corpuscles of a new host, and so the sexual cycle is completed.

Lankester, commenting on the known facts of the developmental cycle, has pointed out that microgametes are true spermatozoa in form, appearance, and *mode of development;* "the production of the sporozoïtes by centrifugal proliferation and the production of a blastophore (residual segmentation mass) characterize them as truly *male cells.*" In this respect the malarial parasite is peculiar. The fission-products of the fertilized cell are not large cells, comparable in size and form to the female cells or macrogametes, but are in form and mode of development identical with male cells or microgametes, and hence when these cells infect a new host and develop into schizonts, we have an instance of parthenogenesis by means of male elements (androcratic parthenogenesis), and not by female elements, as hitherto the only method known.

In the possession of a vermicule stage the malaria parasite comes nearer to the *Gregarinidæ* than they do to the *Coccidiæ,* but they agree with the latter in the possession of a sexual cycle. The cycles of the malaria parasites may be expressed thus:

$$\text{Sporozoïte} \rightarrow \text{schizont} \times \text{merozoïte} \rightarrow \text{schizonts} \times \text{merozoïtes} \rightarrow$$

$$\left.\begin{array}{l} \text{♂ gametocytes} \times n \text{ ♂ gametes} \\ \text{♀ gametocytes} \rightarrow \text{♀ gametes} \end{array}\right\} + = \text{zygotes} \times m \text{ sporoblasts} \times mn \text{ sporozoïtes.}$$

Before concluding our consideration of the systemic position and relationships of the *Hemosporidia* we may briefly enumerate the subdivisions of the *Hemosporidia* themselves, though at present, from lack of knowledge, and more especially of the cycles of development, the classification is only temporary.

ORDER HEMOSPORIDIA.

Suborder.	Genera.
1. Hemosporea.	1. Lankesterella. 2. Karyolysus. 3. Hemogregarina.
2. Acytosporea.	1. "Plasmodium." 2. Laverania. 3. Hemoproteus. 4. Halteridium(?). 5. Piroplasma.
Unclassified	Polychromophilus, Achromaticus, Cytameba, Dactylosoma, Karyophagus, Hemapium, Hæmamœba metchnikovi, etc.

DEVELOPMENTAL CYCLE IN MOSQUITO.

We may here first summarize briefly the characters of the gametes, though the subject is one which requires further elucidation, more especially as to the characters of the young forms. *Malignant tertian microgametocyte* (*male crescent*): (1) The nuclear chromatin occurs in an extensive loose network; (2) the protoplasm stains a light blue only; (3) the pigment is scattered; (4) the shape is kidney shaped, shorter, and broader than the female. *Macrogametocyte* (*female crescent*): (1) The nuclear chromatin occurs in a compact, dense mass; (2) the protoplasm stains a deep blue; (3) the pigment is collected into masses or small rings; (4) the shape is long, narrow, and typically crescentic. According to Maurer, the young gametes occurring in the circulation are characterized by—(1) Their accurate spheric shape; (2) the protoplasm of the parasite is of the same thickness all round; (3) the nucleus forms a portion of the ring and does not project, as in the schizonts; (4) the absence of coarse stippling in the red cells; (5) around the young gametes there soon develops a circumferential red line of stain, as in the adult forms. *Simple tertian microgametocyte:* (1) They are smaller than the schizonts and the females; (2) the nuclear chromatin occurs in a loose tangle, centrally placed or extending across the cell, and is separated from (3) by a clear space; (3) the protoplasm may appear greenish, owing to the fact of its being really stained light blue, while the pigment is greenish (Argutinsky); (4) the pigment is coarser than in other forms (this, according to Schaudinn, is only apparently so). *Simple tertian macrogamete:* (1) They are the largest parasitic forms; (2) the nuclear chromatin is small and homogeneous in character, laterally applied, seldom outlined by a clear space; (3) the protoplasm stains a deep blue; (4) the pigment is smaller in amount and finer than in the males, though Schaudinn says that such differences are apparent only. *Quartan gametes:* The differences in the gametes of the quartan parasites have been little studied, and, indeed, they are commonly exceedingly scanty in the regular types of quartan fever, probably due to the slight immunity acquired against this form, but presumably the differences are of the same character here as generally in the *Sporozoa.*

The differences in the characters of the gametes are very readily observed in the case of *Halteridium* (*H. danilewskyi*) of birds, and are most suitable for a preliminary study.

The technic of feeding and mode of examining mosquitos for various stages of the parasites we shall describe later (p. 215). We will suppose now that an anopheline had been fed on the blood of a patient containing gametes of the malignant tertian parasites,—*i. e.,* crescents,—and it is as well to have made sure by examining fresh blood that the flagellating forms, viz., the male gametes, are present, for if these are present, the female gametes are also present, but it would seem that the converse is not necessarily true. The midgut is isolated from examples killed at various intervals.

Developmental Cycle.—*First and second days:* Fusiform, spindle-shaped bodies are present (vermiculi), which are penetrating the epithelial wall and may have reached the subjacent muscular layer. These spindle bodies have a vacuolated appearance, and the pigment (malarial) is situated for the most part at the blunt end. In stained specimens there is a considerable mass of chromatin centrally placed. *Third and fourth days:* The parasites have increased in size, the protoplasm is more distinctly reticular or vacuolated, the pigment is collected into little granular clumps, and the whole structure is seen to be definitely encysted. *Fifth and sixth days:* The parasites now appear as hernias on the external wall of the gut. They may reach 70 μ in diameter (being generally 40 to 50 μ). The pigment in the later stages has almost entirely disappeared, and the cyst contains a number of highly refractile bodies resembling fat-granules. *Seventh and eighth days:* The large, well-developed cysts now contain large numbers of thread-like bodies, while indications of the formation of these are seen in the previous stage. They radiate from a number of centers. On applying pressure to the specimen the cyst ruptures and large masses of these curved, thread-like bodies—the sporozoïtes—escape into the surrounding fluid. On staining, they are found to possess one or more small masses of nuclear matter centrally placed. They taper at either end, and are about 14 μ in length. If examined in serum, the sporozoïtes are found to have well-marked, writhing movements, and in the case of sporozoïtes derived from the glands, they were found by Christophers and myself, after remaining under the cover-glass overnight, to have changed into bodies indistinguishable from young, "ring-form" parasites, though they were not seen to enter blood-cells, though these had been added.

Brown Spores.—In large cysts found in the stomach-wall are also found structures the nature of which is perhaps still a matter of doubt. Originally noticed by Ross in the proteosoma cysts in the stomach-wall of *Culices* fed on bird's blood containing these parasites, they were termed by him "brown spores." They were originally thought to represent a still further cycle in the life-history of the parasite, and were supposed to be a resistant form capable of carrying on the life of the parasite when the mosquito died and the spores effected their escape into water. But this is purely conjecture, and it seems more likely that they have nothing whatever to do with the parasite but form a quite independent infection of a form of bacterial (or another protozoan) life. These bodies, as described by different observers, vary much in appearance, so that it is evident we have not always the same organism present. Some are typically sausage or banana shaped and dark brown in color. They are found in cysts in which the sporozoïtes have disappeared or have been destroyed by their action. These banana-like black spores have also been found in the region of the salivary gland, though it could not, in the dissection, be said with certainty that they were in the glands. In thousands of *Anophelinæ* dissected by Christophers and myself in India they were encountered only once, and in Africa they were not seen by us. On the other hand, in Italy they appear to be commoner, and their characteristics somewhat different. Thus, in addition to the more or less curved spores, there are others of a brownish-yellow color, almost spheric, showing concentric layers. The size of these is also very variable. By the Italians they are considered to be degeneration products of the cyst contents. Furthermore, in these cysts other *Sporozoa* than the true malarial parasites have been encountered—long oval spores, larger than those which commonly infect the ovaries.

Development of Simple Tertian Parasites.—The *vermicule,* at first clubbed at one end, gradually elongates, and the nucleus becomes centrally placed, while the pigment is irregularly distributed. The forward movement is caused by a secretion of a "gelatinous" substance from the surface, as has been observed by Schaudinn. *First and second days:* The young zygotes are round rather than oval, and are distinguishable by their characteristic pigment as those of the simple tertian parasite, although, as a rule, non-motile. They are also more transparent than those of the malignant tertian. In stained specimens several masses of chromatin appear. The size of the zygote about this date is 10 to 14 μ. *Third day:* The cyst-wall is clearly defined, but is less thick than in the case of proteosoma cysts; the size has increased to about 12 to 16 μ, and the chromatin masses have progressively increased. The protoplasm is vesicular or reticulated. *Fourth and fifth days:* The cysts are visible with low powers as projections on the outer surface of the midgut, and, as in other cases, are most numerous at the posterior end of the gut nearest the origin of the Malpighian tubes. *Sixth and seventh days:* Signs of striation due to the formation of sporozoïtes are clearly visible, and in stained specimens these and the residual segmentation masses can be distinguished. It should be noted that even if the anopheline has been fed only once, the parasites are not all at the same stage of development at the same time, and, according to Bignami and Bastianelli, sporozoïtes may be fully developed in four days, though it takes on an average 8 to 10 days for the sporozoïtes to reach the glands. Brown spores have not been found by the Italians in cases fed on simple tertian parasites. If this observation is confirmed, it is evidently an important one, but probably an insufficient number of cases have been examined.

Development of Quartan Parasite.—It is much more difficult to infect a mosquito with the quartan parasite than with the other species—at least, if we employ for this purpose a hospital case showing a typical quartan temperature-chart, for in these cases flagellating bodies are found with difficulty and are few in number; but positive results have been obtained by the Italians and also by Christophers and myself in India, when, out of 19 mosquitos used, we got in 2 cases positive results. That this difficulty occurs in nature we cannot believe, because in some districts of India the quartan parasite was the only one found by us in the native children, and *Anophelinæ* caught in the native huts were constantly infected.

With regard to the sporozoïtes derived from the various parasites, it is difficult, if not impossible, to distinguish one from another. The developmental cycle requires, in the case of the malignant tertian parasite, an optimum temperature of about 27°, and ceases at lower temperatures of 15.5°–17.5° C. In the case of the simple tertian, however, provided initially a suitable temperature has been maintained, development will still go on at temperatures as low as

12° or 9° C., but the appearance of sporozoïtes is then delayed for twenty-one days. Further, the lowest temperature at which the simple tertian parasite will develop is 20°–22° C., and, in the case of the quartan parasite, 16.5° C. (Grassi).

MOSQUITOS.

The *Culicidæ* or mosquitos or gnats belong to the nematocerous section of the suborder *Orthorhapha* of the order *Diptera*, or flies. Nearly allied families are the *Simuliidæ* or sand-flies, the *Chironomidæ*, or midges, and the *Psychodidæ*, or owl-midges. The relationships of these blood-sucking flies will be evident from the table on p. 131.

We can here define only briefly the characters of the main divisions, treating at greater length the subfamily *Anophelinæ*. For an adequate description of the *Culicidæ*, Theobald's monograph of the *Culicidæ* should be consulted.

Diptera: (1) Two wings. (The posterior wings are represented by a pair of halteres, clubbed structures on a stalk.) (2) They have a suctorial mouth. (3) They undergo a complete metamorphosis, eggs, larvæ, pupæ, imagos.

Orthorhapha: Larvæ have a distinct head. The larval skin bursts to allow the escape of the pupa or imago by a T-shaped opening at the anterior end. These points distinguish the *Orthorhapha* from the *Cyclorhapha*.

Nematocera: Antennæ with 6 or more segments, palpi slender, 4 or 5 segments, thus distinguished from the *Brachycera*, which have short antennæ and palpi.

Chironomidæ: Midges—small slender flies. Wings not scaly. Costal vein does not extend beyond the apex of the wing. Antennæ filiform. Densely plumose in male. Proboscis not projecting. Egg laid in ropes enveloped in mucus. The whole development of the egg in temperate climes takes three to six days.

Psychodidæ (owl-midges): Owl-midges or moth-flies. Minute, densely hairy flies, so easily distinguished. Proboscis short; longer in *Phlebotomus*. Wings in resting position meet like the sides of a roof. The larvæ are cylindric and have a short spiracle. The pupæ have siphons (tubular stigmata).

Simuliidæ (sand-flies): Small, humpbacked flies. Antennæ short, destitute of hairs. Proboscis not projecting. Legs short, with flattened femora. Palpi 4-jointed. Wings broad. All the veins except the anterior ones very delicate.

SUBORDER.	SECTION.	FAMILY.	SUBFAMILY.	GENUS.
Orthorhapha.	1. *Nematocera.*	1. *Blepharoceridæ.*	....	*Curupira.*
		2. *Chironomidæ* (midges).	....	*Ceratopogon.*
		3. *Culicidæ* (mosquitos or gnats).	1. *Anophelina.*	*Anopheles, Myzomyia, Stethomyia, Cyclolepidopteron, Pyretophorus, Arribalzagia, Cellia, Christya, Myzorhynchus, Nyssorhynchus, Lophoscelomyia, Aldrichia.*
			2. *Culicina.*	*Culex, Janthinosoma, Psorophora, Mucidus, Desvoidea, Stegomyia, Scutomyia, Macleaya, Danielsia, Leicesteria, Katageiomyia, Eretmapodites, Skusea, Howardina, Finlaya, Theobaldia, Lutzia, Gilesia, Lasioconops, Melanoconion, Grabhamia, Acartomyia, Tæniorhynchus, Mansonia, Hulocætomyia, Aedimorphus, Verrallina.*
			3. *Megarhinina.*	*Megarhinus, Toxorhynchites.*
			4. *Joblotina.*	*Joblotia.*
			5. *Heptaphlebomyina.*	*Heptaphlebomyia.*
			6. *Aedeomyina.*	*Deinocerites, Aedes, Ficalbia, Uranotænia, Mimomyia, Aedeomyia, Hæmagogus, Wyeomyia, Phoniomyia, Dendromyia, Runchomyia, Sabethes, Sabethoides, Goeldia, Limatus, Hodgesia.*
		4. *Psychodidæ* (owl-midges).	....	*Phlebotomus.*
		5. *Simuliidæ* (sand-flies).	....	*Simulium.*
	2. *Brachycera.*	1. *Tabanidæ* (horse-flies).	....	*Pangonia*, etc.

Both these latter flies will pass through an ordinary mosquito-net, which, however, bars their egress when gorged with blood.

Larvæ blackish, aquatic, about half an inch long, attached to the under side of water-weeds and to stones, etc. The larvæ are cylindric and have "shaving brushes" for sweeping food into the mouth. The larvæ have two pairs of legs. Each pair is greatly modified to form a sucking organ. The motion of the larva is an alternate fore-and-aft one, like that of a leech, produced by means of their suckers. The pupæ build for themselves cocoons attached to aquatic weeds.

Culicidæ (mosquitos): Easily distinguished by the fact that the proboscis is long and projecting. Head and thorax of larvæ distinct; well-developed tracheal system. Eggs laid singly or in rafts.

LIFE-HISTORY OF CULICIDAE.

The Imago.—The perfect insect does not feed for some time (twenty-four hours) after hatching. When first hatched, their wings are soft and they fly but feebly when disturbed. The hatching may be studied by collecting a number of pupæ and placing them in a tumbler. The male is easily distinguished from the female by the long, plumose antennæ. The palpi are also long and hairy in the male, and in some genera expanded terminally, giving the end of the proboscis a characteristic appearance, often of practical use when capturing mosquitos in ill-lighted outhouses, native huts, etc. The commonest mosquitos belong to the subfamilies *Anophelinæ*, *Culicinæ*, and *Aedeomyinæ*. The *Anophelinæ*, which concern us mainly, as they take part in the transmission of malaria, are, without the use of scientific characteristics, readily recognized by the layman.

(1) In the *Anophelinæ* the palpi are as long as the proboscis in the females; in the *Culicinæ* they are quite short in the females. In the *Aedeomyinæ* they are short in male and female.

(2) The *Anophelinæ* can almost at a glance be recognized by their attitude, which is characteristic, though variations occur in the different genera. In the *Anophelinæ* the angle which the proboscis makes with the body is a slight one, 15° in *P. stephensi*, while in the *Culicinæ*, *e. g.*, in the genus *Tæniorhynchus*, it is 45°. The result of this is that the *Anophelinæ* have a characteristic, awl-like aspect, while the *Culicinæ*, etc., are humpbacked. Two only of the *Anophelinæ* so far described have this aspect of the *Culicinæ*, viz., *M. culicifacies*, and [*A*] *culiciformis*, both Indian species.

(3) Hence also the attitude when at rest is different. The body

of the *Anophelinæ* projects from a wall at an angle varying from 5° to almost 90°, while in other *Culicidæ* the body lies nearly parallel, with the hind end closer to the surface than the thoracic end.

(4) The *Anophelinæ* have, as a rule, spotted wings, though there are exceptions to this rule—viz., *A. immaculatus* and *A. aitkeni*, both Indian species; *A. bifurcatus* (Europe), *A. algeriensis*, *A. nigripes* (Europe and America), *A. stigmaticus* (Australia). And, on the other hand, some of the other subfamilies have spotted wings—*e. g.*, in the genus *Theobaldia* of the subfamily *Culicinæ*, *Culex mimeticus* in the *Culicinæ* (in attitude also this mosquito is said to resemble an anopheline), the genus *Lutzia*, etc.

The Ova.—Oviposition was described one hundred and fifty years ago by Réaumur. Miall gives the following account of the process: The mosquito rests the four front legs on the margin of a pool or floating object. The hind legs are crossed, and in the angle between them the eggs are laid; as the number increases the legs become more and more parallel. This description will serve for the method adopted by *C. pipiens*, as described by Taylor. According to Gray, when rafts are being laid and the process is complete, by a movement of the hind legs the raft is tilted so that the eggs stand on end. The egg-rafts of the *Culicinæ* are well-known objects, and are to be found on the surface of uncovered tubs of water, etc., in the tropics. The rafts consist of a mass of eggs arranged vertically, with the pointed end uppermost; the thick end, which contains the head of the larva, lies downward. Little systematic work has so far been done on the eggs of the different genera. We can, however, say occasionally, by examining the rafts, what genus we are dealing with; thus the egg-raft of *Tæniorhynchus* is larger and more slender than that of *Culex*. The rafts vary in the case of *Culex* from one-third to one-fifth of an inch in length, and may contain some hundreds of eggs. Further, according to Taylor, of Havana, considerable differences occur in the size of the rafts and of the individual eggs in various species of the same genus, and, moreover, the eggs of all species of *Culex* are not laid in rafts, but some are laid singly, and in the mode of oviposition also differences occur. Taylor gives the following data: *Culex pipiens:* the rafts contain 200 to 400 eggs; the egg measures 0.9 mm. by 0.16 mm. *Culex nigritulus:* the rafts contain 200 to 300 eggs. The eggs are 0.6 mm. by 0.14 mm. *Uranotænia lowii:* the rafts contain 50 to 75 eggs. *Stegomyia fasciata:* deposited singly. The average number of eggs is 50. The surface of the egg is described by some authors as finely reticulated and having fine air-bubbles attached to it; others describe a rudimentary "float" structure. The eggs of *S. notoscripta* are laid in rafts. Various species of *Culex* and *Psorophora* also lay their eggs singly, *e. g.*, *Culex sollicitans, Culex tæniorhynchus, Culex confirmatus, Culex jamaicaensis, Psorophora howardii.* Further, the eggs of these two latter have laterally well-marked spines. Some species of *Psorophora* and *Mucidus* also lay their eggs singly.

It is in the *Anophelinæ*, however, that we have the most specialized eggs. The eggs are not easily seen in natural pools, except where, as sometimes occurs in the tropics, the whole surface of a sheet of water is one continuous sheet of ova, larvæ, pupæ, and escaping full-grown insects. They may be, however, collected on the surface of wet mud, or they may easily be procured by capturing gravid females in native or other quarters and confining them under a net and supplying a shallow saucer of water, etc. It can then be observed that the eggs are laid singly, but that when they come in contact on the surface of the water, they arrange themselves side by side or in very regular star patterns. With a microscope the floats and frill can easily be observed and differences in the eggs of the various genera can be studied (p. 181). The *Anophelinæ* will deposit their eggs occasionally in a test-tube in the absence of water. They will also lay them in little heaped-up masses on the surface of moist mud. The eggs are at first colorless, but rapidly darken. The resistance of eggs to desiccation is comparatively slight, or, to speak more accurately, we should confine our remarks to the eggs of the *Anophelinæ*. Dried for two or three days on paper in the tropics (temperature, 86°-96° F.), they do not hatch out subsequently (*vide* also p. 183). The eggs of the *Culicidæ*, as a whole, appear to be but slightly resistant to desiccation, but those of *Stegomyia fasciata* are remarkably resistant and will hatch out in water after having been kept dry for as long as three months, and Theobald has also hatched out in England eggs of this species sent him from the tropics. Further, it is stated that eggs laid in October and November (in Europe), which is the latest time for laying, will survive in dry pits and eventually hatch out in the subsequent spring.

Duration of Egg Stage.—The time taken by the eggs to hatch is a variable one, dependent very largely upon the temperature and probably upon the genus and even species of mosquito. In Havana, Taylor gives as the duration of the egg stage for *S. fasciata* twelve to twenty-four hours or longer, *C. jamaicaensis*, twelve hours; *C. sollicitans*, twelve hours; *Ce. argyrotarsis*, one and a half days. Again, the eggs of *Culex pipiens* are stated by Theobald to hatch in twenty hours (temperature not stated). Similarly, Howard, for *Culex pungens*, gives the time as from one night (probably early morning) to 2 P.M. the same afternoon, but in colder weather the time may extend to one or two days, and Giles states that *Culex sp.* eggs take two to three days, but the shorter times are nearer the mark for a temperature of 86° to 96°. It is noteworthy that although eggs normally float, yet in certain species they will still hatch out even if submerged.

Larvæ.—Occur in the tropics in the water-butts around inhabited houses, and their jerky movements downward when disturbed are a familiar sight. These larvæ are mostly those of other subfamilies than the *Anophelinæ*, though the latter also will breed in tins, such as those protecting the legs of tables from white ants; and, as we shall see later, some even of the *Anophelinæ* seem to select the water in tins in preference to the water of streams, pools, or ditches, near at hand. The larvæ of the *Anophelinæ* are readily told from those of other subfamilies by the position they take up on the surface of water: whereas those of the *Culicinæ*, for instance, lie with head dependent and at an angle to the surface of the water, those of the *Anophelinæ* lie flat under the surface film of water and indent the latter. The head of the *Culicinæ* larvæ is relatively large and heavy, and at the hind end they possess a rather long breathing spiracle, the extremity of which comes to the surface. In the *Anophelinæ* this tube is absent, but there is a pair of stigmata on the eighth segment. The flat position, moreover, of the *Anophelinæ* is maintained by a number of paired structures on either side of several of the segments of the larvæ, termed palmate hairs. These are fan-shaped, and when the larva is floating, are opened out, suspending the larva under the surface film. The exact attitude of the larvæ differs much in the different genera, but data on this point are scarce; likewise it should be noted that the *Anophelinæ* do not always float horizontally. When moulting (for larvæ cast their skins three or four times), the position is a dependent one, and from its exceptional characters the larva of *M. turkhudi* always adopts this attitude, but anopheline larvæ can be readily distinguished by the absence of a respiratory siphon and by the presence of palmate hairs.

Larvæ of other flies may, at first sight, be mistaken for Culicid larvæ, especially those of *Dixa*, *Corethra*, and *Chironomus*. The resemblance is, however, only superficial: (1) The *Dixa* larva generally assumes a U shape. The body consists of 11 segments. On the fourth and fifth segments are two pairs of pseudopods, armed with hooks. These structures are not present in the larvæ of the *Culicidæ;* further, there is no siphon tube, but a respiratory cup on the last segment; also some of the posterior segments have dorsal shields. (2) The larvæ of *Chironomus*, or the "blood-worm," consist of a head and 12 segments. The first segment has feet armed with hooks. There are also hooks on the hindermost segment. The last two segments bear small, flexible tubes filled with blood. Moreover, there are two kinds of *Chironomidæ* larvæ: (*a*) Those that live on the surface, possessing no tubule and with colorless blood, the pupæ of which have a respiratory tuft; (*b*) those that live deep in the water, with two respiratory tubules, with red blood, and the pupæ of which have trumpets. (3) The larvæ of *Corethra*, or phantom larvæ, so called from their great transparency, are cannibalistic in their habits and extremely rapid in their almost invisible movements. There are no feet and no respiratory siphon. At the posterior extremity there is a somewhat complex fin structure. The horizontal position is maintained by two pairs of air-sacs, one situated on the thorax, and the other pair on the seventh abdominal segment. (4) Larva of *Mochlonyx:* the air-vesicles are greatly enlarged and the trachea remain pervious, as in *Culex*. It has a respiratory siphon less developed than in *Culex*. The larvæ of the *Culicidæ*, except the *Anophelinæ*, have a long respiratory siphon traversed by the tracheal tubes. The length and shape of this tube differ greatly in the different genera; thus it is long and slender in *Culex;* short and truncated in *Stegomyia*. The siphon is adorned with hairs and spines, which also differ in the various genera, and, moreover, these differences are of specific as well as generic importance. Further, in the shape of the larval head, in the length of the antennæ, and in the characters of their hairs we have a means by which we can certainly differentiate a mosquito (genus) in the larval stage. Thus, in *Culex sp.* there is, at the junction of the middle and terminal third, a tuft of hairs which is absent in *Stegomyia sp.*, while in the latter there is a small single hair about the middle. The antenna of *Stegomyia* is spineless, while that of *Culex* is spiny. Again, the large curved antenna of *Tæniorhynchus* is characteristic, but so far few larvæ have been fully described. The mental plates or lower lip of Meinert are also of generic importance, and the shape of the tooth and its indented margin differ in various genera. These are the main points to which attention should be paid in the description of larvæ.

Breeding-places of Mosquitos.—There is no collection of water, however insignificant, which it is safe to disregard as a possible source of larvæ. There are few places, however dry, where by careful search some unexpected source of water will not be found, and the existence of mosquitos, otherwise difficult to account for, readily explained. From large open sheets of water to the small collections in the hollows of leaves in the jungle larvæ may be found. In concealed cess-pits they may exist in myriads; in covered tanks, in deep wells, in cisterns on the roofs of houses, in the bilge-water of ships, in running streams, in boats, in crab-holes, besides all the well-known sites about domestic dwellings, pots, pans, tubs, etc.—it would be rash to say that there could be no larvæ there; nothing short of careful inspection should determine the point. Larvæ of *Culicidæ* are not infrequently found in brackish water, and *Culex sollicitans* will thrive in sea-water (Taylor).

From deep wells, although mosquitos may be dislodged in crowds, it may be difficult to collect larvæ; as by letting a bucket down the larvæ are disturbed and frequently escape capture, so in inclosed cisterns, such as are used in the tropics for storing water, the proof of the existence of larvæ may require special apparatus; but it is a safe rule to adopt that, when hard pressed, mosquitos will breed in any source of water.

In the detection of larvæ mere inspection is not sufficient, especially if the water contains weeds of any sort. "Dipping" should always be resorted to. A white enameled cup or tin is suddenly plunged beneath the surface, and water and weed are brought up together. A little time is allowed to elapse for the water to clear, and in a minute or so the larvæ come to the surface. Weedy ponds, which to the closest inspection show nothing, when searched in this way often yield many larvæ. On the contrary, many promising pools yield no larvæ at all. The explanation often lies in the fact that they contain small fish. Again, ponds covered with species of *Lemna* are often free from larvæ. Not only fish, but a variety of water creatures prey upon larvæ, and yet where both fish and these predatory enemies exist, larvæ may also exist, provided there is a sufficient supply of coarse water-weed to protect them from the view of their enemies. Not only have larvæ many enemies, but they are also cannibalistic. In fact, not only do the different species prey on each other, but also the large members of one species will devour the small ones. It would appear, also, that some larvæ are almost entirely cannibalistic—*e. g., Psorophora sp., C. concolor, Mucidus scataphagoides, Megarhinus sp.* Larvæ are frequently absent from large open spaces of water, and not infrequently from deep waters. They also do not appear to frequent clear cool spring water. They are difficult to find in moving water, *e. g.*, where a lagoon is affected by the flow of the tide.

In some places they are not found in the cement containers surrounding fountains, though in a cement tank in a shady garden, especially if it contains rotting leaves, larvæ may abound. Again, of two tanks, one made of metal and the other of wood, it is the latter that is most likely to contain larvæ, and in the wooden tubs used by natives for storing larvæ in the tropics they exist often in amazing numbers, so that a native village may produce literally millions of insects (chiefly *Stegomyia*). Anopheline larvæ put in a collecting bottle and exposed to the shaking of a long transit often appear dead, and they sink to the bottom of the water. They may, however, often be revived by carefully floating them out on the surface, when, shortly, signs of movement will be exhibited.

Duration of Larval Stage.—Taylor gives the following data: *S. fasciata*, minimum, six days; *Culex confirmatus*, four and a half days; *Culex jamaicaensis*, three and a half days; *Culex sollicitans*, four and a half days; *Cellia argyrotarsis*, twelve days. The larval stage of *Megarhinus sp.* is, however, considerably longer, lasting fifteen to twenty-one days (and the pupal stage six days) at a temperature of 80° to 90° F. The shortness of these periods is remarkable, for Christophers found for *Stegomyia sp.* in India, where the temperature of the water was 96° to 102° F., that the duration of the larval stage was seven days, pupation taking place on the eighth day. For *M. rossii* Christophers gives eleven days as the duration of the larval stage, with pupation on the twelfth. These longer periods for the two anophelines noted above are very interesting, and extended observation on this point is necessary.

Nymphæ.—The nymphæ are the globular headed, comma-shaped bodies into which the larvæ develop. They have a "tail" more or less curved under the head. They are not so easily seen as the larvæ, and readily take fright, diving rapidly to the bottom, whence they arise again in a series of skips and hops. The differences between the nymphæ are not so great or so readily perceived as in the case of the larvæ. The main differences exist in the shape of the siphon tubes, a pair of which project from the bulbous thorax. These differences can be appreciated only by microscopic examination. In the *Anophelinæ* the siphons have a square, truncated end, and are shorter than those of *Culex*. The siphons of *Culex* are long and narrow and have a slit-like opening. In *Stegomyia sp.* the siphons are broadly triangular and are very characteristic. Differences occur in many other genera, and many of the genera are still undescribed. The nymphæ that may be most easily confounded with those of the *Culicidæ* are those of *Chironomus* and *Corethra.* That of *Chironomus* is characterized by its conspicuous respiratory tufts. The pupa lies at the bottom of the water, with only the tufts and thorax projecting. The pupa of *Dixa* has not been very fully described: it has a general resemblance to that of *Culicidæ* pupæ. A close inspection would probably recall many points of difference. The "head" of the pupa of *Corethra* is not so bulbous as that of the *Culicidæ,* and the tail fin is broader. The trumpets are pointed, with a slit-like opening. The pupæ of the sand-flies (*Simuliidæ*) lie concealed in cocoons attached to water-plants, the respiratory tufts only of the pupa projecting.

The pupa of *Tanypus* also resembles that of the *Culicidæ.* The respiratory trumpets are long and cylindric. The pupa, however, remains mainly below the surface, attached by its (armed) tail. Further, it has suckers on the dorsal side of the abdomen.

Duration of Pupal Stage.—Taylor gives the following data: *S. fasciata,* minimum, two days; *C. confirmatus,* two days; *C. jamaicaensis,* two days; *C. sollicitans,* three days; *Ce. albipes,* two days.

Emergence of the Imago.—As the time approaches for the emergence of the imago the pupa becomes less active, and if disturbed, will not dive far below the surface. Silvery streaks due to air appear on the dorsal surface, and the pupa becomes extended, lying beneath the dorsal-surface film. A crack appears in the chitinous coat, and the thorax of the mosquito, with its head bent back underneath, emerges. Then follow the wings and abdomen, while at this time the extremities of the legs still remain in the pupal case, and it is at this stage particularly that the process occasionally fails, for the legs remain attached to the pupal skin, and the mosquito cannot free itself, but in its struggle is eventually drowned. If the process proceeds normally, the head gradually is unbent and the legs drawn out, the front legs bending forward and upward at the "knee-joint," and the hind legs backward and upward. The fly, when first hatched, rests quietly on the surface of the water, or, if disturbed, does not fly far. The wings, however, harden sufficiently for flight in about five minutes, but it is not until considerably later—some hours probably—that they attain their normal character.

Celli gives the duration of the complete life-cycle as thirty to thirty-two days "in the favorable season," and states that from April to September there are ordinarily four or five generations.

Ficalbi has calculated that in four generations from the mother stock two hundred millions would be born. This period is greatly in excess of those given by Taylor, whose observations were made in Havana. He gives as the period from egg to winged insect: *C. nigritulus*, minimum, nine days; *C. confirmatus*, seven days; *C. jamaicaensis*, six days; *C. sollicitans*, eight days; *Psorophora howardii*, six days; *Ce. albipes*, seventeen and a half days; *U. lowii*, eight and a half days.

Fecundation of Mosquitos.—This takes place soon after the emergence of the imago, so that it is rare, according to Taylor, to find an unfertilized female. Pairing takes place in sunshine, and the male is described as taking an inferior position, by some, while others describe the male as seizing the female. Annett and Dutton have described swarms of males (anophelines) dancing in midge-like fashion in the evening. Eggs are laid even by unfertilized females, but they do not develop into larvæ.

Length of Life of Mosquitos.—In captivity they may be kept alive for as long as six months if provided with sugar, dates, bananas, or sherry and water, etc. In nature it would be safe to assume that their life is even longer; the hibernation of anophelines we shall consider later.

Time of Biting.—Though the *Culicidæ*, more especially the *Anophelinæ*, on the whole, are nocturnal in their habits, yet many bite during the day-time, and in fact not at night. Thus *S. fasciata*, Durham states, begins biting about sunrise, 6 A. M., but mainly from 12 o'clock noon to 2 P. M., while from 3.30 P. M. to 5 P. M. they cause little trouble, and after dark they are not met with. Ficalbi states, with regard to the same species, that it attempted to bite on the second day after hatching; succeeded in doing so on the third day; it then took three days to digest the meal, and on the fourth day fed again. Taylor states, however, with regard to *S. fasciata*, that it will bite during the day or night if hungry. *C. confirmatus*, *C. tænio-rhynchus*, etc., also bite day and night; *Cellia albipes* will also bite during the day.

DISTRIBUTION OF CULICIDAE.

The distribution of the *Culicidæ* is practically "world-wide." From the tropics to the polar regions they are encountered, and in such desolate regions as the tundras of Siberia they occur in countless myriads. It is probable that these *Culicidæ* of cold regions do not belong to the subfamily *Anophelinæ*, and, on the contrary, it is probably true that the *Anophelinæ* are especially numerous in the tropic regions of the earth.

Migratory flights of *Culicidæ* have been described, but they are a rare phenomenon, and during the last few years that particular attention has been directed to them, no similar occurrence has been noted. These flights were observed in Victoria, Texas, U. S. A. They occurred after a strong easterly wind had been blowing for some days, when a cloud of mosquitos flying about 50 feet above the ground appeared. The "flight" was about three miles wide and lasted for about five days, following the course of the wind. The flight probably originated in a marsh 35 miles away. A second similar flight occurred seven years later. The flight was about 10 feet above the ground and extended to a distance of about 60 miles. Such a phenomenon is undoubtedly exceptional, and, as we shall see, there is good reason to believe that, under ordinary circumstances, the normal flight of mosquitos is very limited,—to be measured in yards rather than miles,—and that mosquitos have a distinct aversion to wind. Our own experience has often confirmed this point. On the west coast of Africa, when a stiff land-breeze was blowing, one could sit in one's bungalow free from the attacks of *Stegomyia*, and if a tornado was raging, there was no sign of mosquito life.

On the other hand, in addition to migratory flights, there is a certain amount of evidence to show that mosquitos may fly as far as 20 miles if a steady wind sets in a particular direction, mosquitos having been encountered out at sea that distance from land; but, in my opinion, most of these statements require to be received with caution, as it is not at all improbable that the source of the mosquitos lies in some overlooked place on board, in some uncovered water-butt or some recently opened hold.

That mosquitos travel in railway trains may daily be observed in the tropics, but that the few introduced into a locality in this way could be the cause of their appearing where previously absent is exceedingly doubtful. Many of the older statements about mosquitos must be received with great caution, as it requires an expert to detect all possible breeding-places, and a statement by a non-expert that mosquitos are absent from a place must be examined very carefully. That mosquitos have ever been introduced by ships or railways from one continent to another there is no evidence to show, and, in fact, the well-defined areas of distribution of the *Anophelinæ* are against this. Certainly it would be an interesting experiment to make, *e. g.*, the transportation of an Indian anopheles to

Africa, and vice versâ. We shall consider some of these points more in detail when we come to the *Anophelinæ*.

ANATOMY OF THE MOSQUITO.

The true proboscis in the *Anophelinæ* is concealed by the maxillary palpi, which lie slightly dorsal to it. The maxillary palpi in the female consist of five segments. The first or basal segment is extremely minute, and is disregarded by some authors, who consider the female palpi to have four segments and the male three. This is of some importance in systematic classification, for the real second segment would be called the first, and so on. The second segment is long, but not so long as the third segment, which is the longest of all. The fourth segment is shorter than the second, and the fifth or terminal segment is little more than twice as long as broad. These segments are often incorrectly termed joints. This term, however, should be reserved for the point of junction of two adjacent segments, and it is at these joints or at the tip of the last segment that the "bands" are formed which, as we shall see, are of great assistance in separating closely allied species. The palpi are scaled, but the amount of this varies greatly in the different genera of the *Anophelinæ*, *Anopheles*, for instance, having few, while *Cellia* has very many. The shape of the palpi in the male differs from that of the female in that the ends are broad and club-shaped, and their appearance is so characteristic and so prominent in the living *Anophelinæ* that the male can be distinguished in dark dwelling-houses more readily by this sign than by its plumose antennæ. In the case of the male palpi, while some authors describe five segments, the two last of which are expanded, others only describe three, *i. e.*, one besides the two terminal segments, the constrictions of the basal segment being ignored. During the act of sucking blood the palpi project upward, away from the proboscis, at about a right angle. The proboscis itself consists of seven parts. The labium forming the sheath of the proboscis is grooved on its dorsal surface, and it is in this groove that the rest of the structures—the stilets or those portions that really traverse the skin—lie. It is slightly longer than the true proboscis, and has two short segments, attached distally, known as the labellæ; these are movable on a hinge-joint. The labium itself is continued dorsally still a little further than the level of these joints as a fine tongue, just as a pen is prolonged beyond the end of its holder. Further, Dutton describes a fine membrane covering in the area between this extended tongue and the base of the labellæ. This median portion of the terminal segments of the labium bears hairs and is tightly pressed against the skin during the act of sucking, while the labellæ are expanded and support the proboscis laterally. The labium and its labellæ do not pierce the skin, but the stilets pass through and receive guidance from the expanded labellæ, as the fingers of a billiard-player guide the cue. During the act of suction, as the stilets pierce, the labium bends with its convexity ventralward, as a cane walking-stick bends when pushed against the ground, and the angle of flexion may be distinctly acute, depending on the depth to which the stilets are inserted. The labium is, as we have said, comparatively large and fleshy, and is traversed by nerves, tracheæ, and muscle-fibers. It is in this fleshy portion that *Filariæ* may be encountered, and much discussion has arisen as to how they find an exit. It was originally supposed that the labium was ruptured during its flexion, and that the filarial embryos made their exit thereby, but there is no evidence of any such rupture, and if, as has been generally assumed, the filarial embryos are in the labium, with the object of reaching the blood during suction, they would not attain this end by escaping at this point. The filarial embryos, moreover, have their heads abutting on the end of the labium,—in fact, in the region of the thin membrane described above,—and it is here, according to Dutton, that they escape. As the proboscis is retracted the labium straightens out again, and, in fact, by its resiliency, as Schaudinn suggests, probably aids in bringing about this process. Turning now to the parts that actually pierce the skin, *i. e.*, the stilets, we have six structures—two tubular structures, the epipharynx and hypopharynx, two pairs of chitinous rods, the maxillæ, and the mandibles.

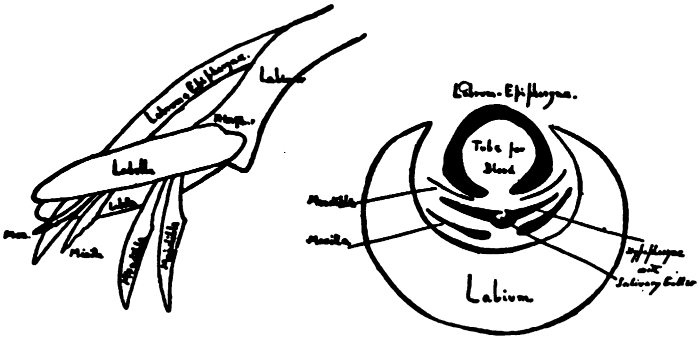

FIG. 5.—THE PROBOSCIS SHOWING LABIUM AND STILETS ON THE RIGHT, THE PROBOSCIS IN CROSS-SECTION; THE PALPI ARE NOT SHOWN (from Stephens and Christophers' "Practical Study of Malaria").

The upper lip, or labrum epipharynx, consists of two parts intimately fused together, of which the labrum is the most dorsal. It arises at the base of the clypeus, while the epipharynx is a hollow tube not completely closed on its ventral side, continuous through the base of the clypeus with the pharynx. In its passage through the anterior portion of the clypeus the borders of the epipharynx are reflected upward and outward so as to become continuous with the lateral walls of the clypeus. It is the longest of these structures, and its extremity, slightly decurved, resembles somewhat the point of a hypodermic needle. At its base the epipharynx is continuous with the buccal cavity, and it is through this tube that blood passes up during the act of suction. Closely applied to the ventral opening of the labrum is the hypopharynx. The hypopharynx is flat or crescentic in shape, the middle of the crescent being thickened, and in this part there is a groove or gutter which, by others, is figured as a complete perforation. It is in this groove that the continuation of the salivary duct runs and along which malarial sporozoïtes pass out. Basally, the hypopharynx has attached to it two powerful muscles which probably serve to retract it after insertion. In the male mosquito the hypopharynx is blended with the labium, forming its dorsal surface; it is also traversed by a salivary duct, but in the male, except rarely, the proboscis does not pierce. The epipharynx and hypopharynx are closely applied to each other and mutually close the incomplete passages in both. The remaining organs are the paired mandibles and maxillæ. Their position is dorsolateral. No doubt the exact position and size of the parts will vary in different genera, and, in fact, differences occur in the genera *Culex* and *Anopheles*. The most dorsal are the mandibles; they lie, one on either side, external to the labrum. They are more delicate than the maxillæ. In cross-section they are crescentic, and at their extremity they are provided with about 30 teeth (*Anopheles maculipennis*). There are no mandibles in the male. The maxillæ lie dorsoventrally and partly embrace the edges of the hypopharynx. In cross-section they are approximately wedge-shaped, with the thick edge of the wedge ventral and inward; the extremity of the maxillæ is also toothed, but the teeth are coarser than those of the mandibles and are fewer in number (13 in *Anopheles maculipennis*). From the base of the maxillæ with which they are articulated arise the maxillary palpi described above. The apodemes with which the palpi are articulated are described under Muscular System. In *Culex pipiens* the structure of the parts, as described by Schaudinn, is slightly different.

He figures the maxillæ as lying dorsal to the mandibles, and thicker and more triangular in cross-section than the latter. The "saws" on the maxillæ and mandibles have their points directed backward, so that they tend to fix the proboscis in position when inserted.

The Act of Suction.—The mosquito can be seen feeling with its labellæ various portions of the skin, then, when one is selected, the labellæ expand and the "tongue" is applied to the surface. By this time the palpi have moved out of the way. The point of the labrum now appears between the extended labellæ and pierces the skin. At the same time the mandibles and maxillæ can be seen working up and down, and the head of the mosquito rocks somewhat in its efforts to saw out the aperture. The proboscis then sinks in, up to half or even almost the whole of its length. During this time the proboscis is held at right angles to the body or directed slightly forward. The hind legs of the mosquito (*C. pipiens*) may have been, in the mean time, lifted off the skin and bent back above the abdomen, so that the mosquito rests on its front pair of legs only. The substance which causes the irritation accompanying the bite is injected at the beginning of the process, for if, as not uncommonly happens, the mosquito flies away before sucking blood, the irritation is felt notwithstanding. The whole process of feeding lasts two to three minutes. It may be worth mentioning here, a fact well known to residents in the tropics, that a mosquito feeding on the back of the hand may be trapped by folding the fist and so tightening the skin.

Alimentary Canal.—The constituents of the alimentary canal are: (1) The foregut, comprising—(*a*) The mouth; (*b*) the pharynx; (*c*) the esophagus. (2) The midgut, comprising—(*a*) The homologue of the proventriculus; (*b*) the so-called stomach; (*c*) the pylorus. (3) The hind-gut, comprising—(*a*) The pylorus; (*b*) the ileum; (*c*) the colon; (*d*) the rectum. We have, in addition, the following appendages of the alimentary tract: (1) The salivary glands; (2) the esophageal diverticula; (3) the Malpighian tubes.

The mouth parts we have already described; we shall now take in order the soft parts of the alimentary tract.

The pharynx extends from the base of the proboscis to the origin of the esophagus, at the point of junction of the head and neck. It is, in fact, the continuation backward of the upper lip (labrum) or epipharynx above and the hypopharynx below. It is lined throughout its extent with chitin. It can, for practical purposes, be divided into two parts: (1) A narrow portion, passing upward and backward and ending opposite the furrow which separates the clypeus from the head; (2) a horizontal portion, approximately at right angles to the former. This passes between the supra-esophageal and infra-esophageal ganglia and their commissures, and terminates in the esophagus, at the junction of the head and neck. In this second dilated portion the walls are modified so as to form a pumping organ. In the anterior portion specialized structures have been described by Dutton and Schaudinn, but there is some disagreement in the descriptions. Firstly, Dutton states that it is only the anterior and posterior portions of the upper wall of this portion that are chitinized, the remaining middle portion being covered with flat epithelial cells, whereas Schaudinn and Christophers do not mention this layer. Again, according to Dutton, there exists, on the anterior portion of the upper wall, a few low conic papillæ (taste papillæ), while of these Schaudinn makes no mention; the latter, however, describes on the floor of the first portion of the pharynx, without more precisely defining the exact spot, a peculiar arrangement. The chitinous layer is, he says, traversed by fine canals arranged at right angles to the surface. In each of these canals there exists a cell, hair like in form, each connected with a nerve-fiber of the inferior esophageal ganglion; from this we may infer, however, that the structures lie near the junction with the second portion of the canal, for this is the position of the ganglion. On reaching the horizontal portion it is only the free end of these cells that projects in the form of exceedingly fine papillæ. Schaudinn considers that this structure functions as a taste organ. Dutton describes this organ as situated at the point of junction of the first and second portions, where, as a matter of fact, as pointed out originally by Dimmock, the dorsal and ventral walls approximate, causing a constriction which probably serves as a valve to prevent the return of fluids to the mouth during the action of the pump. It is at this point that Dutton describes the existence of this organ. It is situated on the posterior end of the ventral chitinous plate. It consists of a ridge of stout, hair-like processes, which curve forward so that their tips lie in the angle between the upper surface of the first and second parts of the pharynx. The hairs are of two kinds—an anterior large set, probably a single row, and a posterior small, fine set, situated in a clump immediately behind the former. The larger hairs consist of a short stout shaft firmly embedded in the chitinous pharyngeal wall; this shaft supports a cup with a free rim curved outward; within the cup lies the oval-shaped bulbous extremity of the base of the hair. This bulbous extremity contains a single large cell. The remaining free portion of the hair curves forward and tapers to a fine point, and appears to have a central shaft inclosed within a chitinous cuticle, from which barb-like processes project. The hairs of the posterior set are much finer and shorter and are more numerous; they appear to be simple in character. In transverse section this structure presents to some extent the appearance of "rods and cones." The subesophageal ganglion lies in close proximity to this structure, but no nerve-fibers have been shown to communicate with these specialized hairs, although such probably exist (Schaudinn, we have seen above, describes them). That, in the first place, these hairs act in conjunction with the general conformity of this part of the pharynx as a valve to prevent the regurgitation of blood back into the mouth during the action of the pumping organ seems to admit of no doubt; on the other hand, such specialization in structure would lead one to suppose that they possess also a sensory function.

The Pumping Organ.—After passing through the ganglionic ring formed by the supra-esophageal and infra-esophageal ganglia the pharynx widens into the large chamber, the pumping organ. In cross-section here the lumen of the pharynx, in the position of rest, is triangular. This is caused by the deposition, in its walls, of three thick chitinous plates, one on each side and one superiorly. The plates are connected by a thinner (non-chitinous) membrane, and their edges are inrolled, so that when extended by the muscles acting upon them they return with spring-like force to their original position. Three sets of muscles are inserted into the sides of the pump: A dorsal pair of muscles, arising from the occiput, and two lateral masses attached to the lateral portions of the inner surface of the head. Beyond the pumping organ the cavity of the pharynx agains narrows, and there are here a distinct bend and thickening of the muscular wall, where the pharynx joins the esophagus. This portion functions as a valve, so that when the pump is in action, blood is drawn into its cavity by the vacuum formed, the posterior valve leading to the esophagus being then closed. When the pump contracts, this opens and blood flows into the esophagus, its forward motion being also promoted by peristaltic movements from before backward of this muscular portion and of the commencing portion of the esophagus. The return of blood into the mouth is prevented by the sharp angle (and the presence of the hairs, according to Dutton) which exists at the junction of the ascending and horizontal portions of the pharynx.

The esophagus begins immediately behind the posterior pharyngeal valve, and after a neck-like portion, forms a sac or reservoir which, according to Christophers, does not possess a chitinous intima, but does, according to Schaudinn. The epithelial lining of the first portion is subcylindric or cubical; that of the reservoir, subcubical, while in the diverticula the epithelium becomes quite flat. The muscular covering of these portions is also slight, while in the esophagus it is less than in the pharynx; in the diverticula there remain only a few scattered fibers. Besides the neck and main sac or reservoir of the esophagus we have as appendages of the esophagus the most interesting structures, known as *diverticula* (or sucking stomachs of some authors). They are readily seen in all dissections of mosquitos, and in hibernating mosquitos (in England) have a striking appearance, from the mass of bubbles of gas with which they are packed. These diverticula are usually three in number—a large ventral one and two smaller lateral ones. In the newly hatched mosquito the ventral diverticulum is small, but soon becomes expanded, and stretches into the abdomen as far back as the fifth abdominal segment. It not uncommonly happens, too, that a diverticulum may be wanting, being represented only by a slight pouching of the esophagus. The function of these diverticula is a somewhat disputed point. It can hardly be doubted, however, that it has something to do with the contained bubbles. Christophers has assigned to them mainly a physical function in supporting the pressure of the blood in the stomach. But Schaudinn's experiments throw new light on the subject. Any one can satisfy himself, moreover, that these diverticula often contain large masses of bacteria besides protozoa. The fact of the presence of these bacteria led Schaudinn to suppose that the gas was not air, as had been generally supposed, but carbonic-acid gas. This was easily shown by adding baryta water to the preparation under the cover-glass, when a turbidity followed. Schaudinn then supposes that the function of the gas is to prevent coagulation of the blood during the act of suction. But to this point we shall return. Another function that has been ascribed to these diverticula is that of blood reservoirs, but there is little to support this, as at the end of the sucking act the diverticula contain at most a few corpuscles. To proceed, however, with the anatomy of the gut. After the diverticula have been given off from the esophagus we reach the junction of the esophagus and midgut. This portion is considered by Christophers to be the homologue of the proventriculus found in many insects.

The Proventriculus.—This consists of a fold of the fore-gut into the midgut, and presents some interesting features. The extent to which this invagination occurs differs according to whether or not the insect is feeding. In the fasting insect the infolding is considerable, and the infolded portion is thrown into a number of secondary folds. Moreover, at the point where the esophagus merges into the midgut there is a considerable development of muscle-fibers, so that a sphincter is formed. This, together with the invagination, forms an efficient valve. This valve is opened when blood is being taken in; the invaginated portion is drawn out, the longitudinal muscle of the esophagus contracts, and the invaginated portion, now unfolded, is expanded by the entering blood and thus forms a "crop." The peristaltic movements of the esophagus then pass the blood on into the midgut. Another peculiarity of this "crop" described by Schaudinn is that the epithelium secretes a kind of jelly-like layer which covers the mass of ingested blood, so that the food, as in other insects, is not in direct contact with the epithelium itself. While, then, in the fasting condition the beginning of the midgut and the necks of the diverticula are in apposition, in the feeding insect the necks of the diverticula are separated from the midgut by the region occupied by the drawn-out invaginations, or, in other words, the crop.

The midgut extends from the proventriculus to the point of entry of the Malphigian tubes. It consists of an anterior thoracic narrow portion and a larger abdominal posterior portion, the so-called stomach: this latter becomes greatly distended after feeding. The convexity of the anterior portion lies dorsalward, so that the ventral is shorter. While Christophers states that the cecal tubes or appendages found in many insects in the anterior portion of the midgut are absent, Schaudinn says in *Anopheles* a considerable number are always present, but that in *Culex (pipiens)* they are only slightly represented.

Histology of the Midgut.—The epithelium consists of a single layer of large cells, columnar in the fasting insect, but flattened when the stomach is distended. Their most striking feature is the clear, striated border which is characteristic of the midgut epithelium, for it is not found elsewhere. In the distended organ this appearance is wanting. The cells are granular and stain deeply with hematoxylin. The granules are collected mainly toward the free border of the cell, and are especially well seen in the anterior portion of the midgut. Besides the granules, there occur a number of vacuoles or drops which also are best developed at the free border of the cells. The cells are evidently glandular in character; they have, besides, a deeply staining nucleus, centrally situated. The muscular layer of the gut is less well developed than in the midgut. It consists of an open meshwork of fibers running longitudinally and circularly, forming, especially in the posterior portion, a regular arrangement of rhomboidal meshes. The muscle consists of long, fusiform, striated fibers. It is embedded in a certain amount of connective tissue containing also elastic fibers. Besides these layers we find, on the outside of the gut, numerous *tracheal cells* or large fusiform cells in which the tracheæ end. The midgut ends in a marked constriction, formed by a development of muscle-fiber forming a distinct pylorus.

The Hind-gut.—This commences at a point which corresponds externally to the junction of the sixth and seventh abdominal segments, and is the point at which the five Malpighian tubes enter. It is divided into three portions: (*a*) *The ileum,* a dilated portion in which the muscular layers are strongly developed, while the epithelium is flat; this passes insensibly into (*b*) the *colon,* which is the longest and thinnest portion of the hind-gut. It passes dorsalward and then descends centrally again, forming a broad, open curve. It then narrows, finally dilating into (*c*) the *rectum.*

Histology.—The whole of the hind-gut is covered with a chitinous cuticle. This is most strongly developed in the first part, viz., the *ileum.* From the muscular layer proceed ingrowths between the epithelial cells, producing thickenings of the chitinous cuticle, giving the gut a characteristic thread-like appearance. Into the rectum project about six so-called rectal glands. They are really conic outgrowths of the epithelium.

The Malpighian tubes opening at the junction of the midgut and hind-gut are five in number. They pass forward in loops above their origin, their blind ends being attached in the neighborhood of the rectum by tracheal branches. They are composed of granular cells, with a large, deeply staining nucleus. The cells are alveolar in structure, the alveoli being arranged at right angles to the lumen of the tube. During the resting stage they contain fluid, while during secretory activity they contain spheric granules which are passed out into the lumen of the tube. The lumen is a fine, spirally arranged tube. The spiral arrangement is produced by the alternate bulging of the cells of the Malpighian tube, so that at one level practically only one cell is seen cut across, the others being flattened and displaced, the lumen being also displaced by the bulging, to reappear at the other side when the cell of the opposite side bulges.

Salivary Glands.—These are intrathoracic structures lying close up against the prosternum. They consist of six tubular acini, three lying on each side, and are just visible to the naked eye in dissections, being about 1 mm. in length. The acini lie one above the other in the long axis of the body. The upper and middle acini at their distal ends almost touch the proventriculus, while the lower acini lie close to the conjoined thoracic ganglia. The ventral diverticulum of the esophagus lies between the acini on either side. The acini themselves lie embedded in portions of the fat body. Each acinus is traversed by a duct. These three ducts at the base of the acini widen, to form a common duct. This duct passes upward to the neck and meets its fellow from the other side beneath the subesophageal ganglion. They then unite to form a common duct, which passes forward and enters the salivary receptacle which lies at the base of the labium. This is a hollow, cone-shaped structure, with its apex pointing forward and downward. It is chitinous in structure, though the wall is thin and transparent on the dorsal surface and its basal wall is still more membranous. This receptacle is acted upon by muscles on either side arising from the ventral surface of the lower chitinous plate of the pharynx. By their contraction the cavity is dilated and saliva can flow in during relaxation, the walls of the receptacle or pump probably resuming their original condition. The apex of the receptacle passes upward and enters into the hypopharynx by a V-shaped opening, at the point of origin of the latter from the ventral chitinous wall of the pharynx.

The acini, though usually three in number in most genera, are five in number in *Psorophora.* They may become bifid at their extremities, and it is not uncommon to find a small accessory acinus given off from the basal portion. Each gland is composed of a single layer of cells lying on a basement membrane; the cells are bounded internally by the wall of the intraglandular duct. The course of this duct is somewhat different in *Culex* and *Anopheles;* while in the latter there is a dilatation near the base of the duct, in *Culex* this is not so, but it remains of the same caliber throughout until it opens into the extraglandular portion. The extra-acinar duct is a thick-walled tube bearing a spiral chitinous thread in its internal layer. It has a superficial resemblance to a trachea, and has been mistaken for this structure. The main ducts leaving the acini are lined with an apparently homogeneous but nucleated intima. The character of the glandular epithelium varies in the different acini, both in *Culex* and *Anopheles;* they have been termed by Christophers the granular and the clear type respectively.

The Granular Type.—The granular appearance in the stained cell is caused by an accumulation of secretion by which the nucleus is displaced to the periphery of the cell. This secretion in the fresh gland exudes from the cell in clear, refractile globules. The appearance is then an artificial one. In the hardened gland the majority of the cells have this fine granular appearance, but in some of the cells of the terminal portion of the acinus a few globules only of secretory matter may be evident. These granular cells do not stain deeply with hematoxylin, and the nuclei, pushed to the periphery, show apparently signs of degeneration. The portion of the acinus lying near the duct may, however, show considerable variation from the type in the case of *Anopheles*. The cells are smaller; the nucleus and protoplasm are displaced to the periphery by a clear body in the center of which is a dark area continuous with the duct lumen. This is not always present in *Culex*. In the latter, however, in the same portion of the gland, that is, the portion nearest the duct, the epithelium may be columnar, with centrally placed nuclei and no secretory substance. Sporozoïtes occur in all three acini in *Anopheles*, but, according to some observers, most abundantly in the central lobe. The secretion of the cells of the acini passes into the lumen by means of minute openings into the cell.

The Salivary Muscle.—A band of muscle arises close to the origin of the first pair of legs and passes outside the salivary gland on either side. It is probable that the contraction of these bands would exert pressure on the glands and so promote the excretion of saliva.

The Irritation of the Mosquito Bite.—Before considering this question, on which Schaudinn has made some interesting experiments, it will be necessary to return to the esophageal diverticula. Besides the gas-bubbles which they contain, there are also present a trace of fluid and also bacteria, or "molds." They are always present in greater or less quantity. Before sucking they are few, but while digestion is going on in the stomach they increase immensely, forming a thick layer over the wall in all stages of proliferation. Even in the newly hatched mosquito they can be found, and, in fact, in the egg, in the larvæ (in the gut), and in the nymphæ. Where scanty, as in the newly hatched mosquito, they can be developed in large quantities by feeding the mosquito on sugar solutions, and Schaudinn was led to believe that they were the agents which produced the carbonic acid with which the diverticula are filled. When a mosquito is thus fed on sugar solutions, the gas-development sometimes reaches such a pitch that the gut is enormously distended with gas and death of the mosquito may ensue. Such mosquitos are often seen in the tropics; they look as if they were suffering from some emphysematous affection. Schaudinn next observed what took place when an insect punctures. This may readily be studied under the microscope by confining the mosquito under a watch-glass or other suitable transparent covering. Observed under the microscope, the respiratory movements of the mosquito are seen to be going on regularly and moderately. Suddenly a violent contraction of the whole abdomen sets in, which it is interesting to observe is not seen if the mosquito is feeding on fluids of any kind. What, then, is the meaning of this enforced contraction? Schaudinn supposes that it is induced by the presence of carbonic-acid gas, which is present on the superficial layers of the skin, and that it leads, by its presence in the tissues when inspired through the stigmata of the body, to violent muscular contraction. This idea he sought to confirm experimentally by confining a mosquito in a hollow slide and then producing an atmosphere of carbonic-acid gas by the addition of acid to some particles of chalk placed in the hollow slide. This violent contraction he was actually able to bring about occasionally in this way. What, now, is happening in the pharynx and proboscis? This can be readily studied at the same time by carefully confining the proboscis under a cover-glass in a drop of fluid, such as glycerin or salt solution. Observing under the microscope, it is then seen that during this violent contraction of the abdomen the gas-bubbles of the diverticula are extruded from the tip of the proboscis, and, together with them, large quantities of the "molds" that the diverticula also contain. Probably at the same time the secretion from the salivary gland also reaches the site of puncture, when the mosquito is piercing the skin, the flow being promoted by the pressure of the salivary muscle on the glands. These substances have then been ejected; and, if the process is further watched, it is seen that they float away from the tip of the proboscis; but (and this is a very important fact), both gas-bubbles and bacteria may be sucked back again almost completely. What is the function of these secretions? It has always been taken for granted that the irritation of the mosquito puncture is due to a drop of "poisonous" saliva injected into the wound, and that probably an additional function of the saliva was to prevent the coagulation of the blood in the same way as it is generally accepted that the secretions from the pharynx of a leech act on the blood during the process of sucking, but Schaudinn's observations lend no support to this view; for if the saliva has this function, then presumably, by isolating the salivary glands and rubbing them into the skin in a superficial wound, the irritative effect should easily be got. The glands, as we shall see under the section Technic (p. 217), are easily isolated, and they may be rubbed up in a little salt solution and then rubbed into the wound. The result is entirely negative: no trace of the irritative effect and reddening is obtained. Experiments have been made also by Schaudinn and others to test what the action of the salivary secretion is on the blood. The results are somewhat contradictory, some observing no trace of a hemolytic effect, whereas Schaudinn obtained some evidence of this. As to any anticlotting power, the experiments are also not conclusive. The esophageal diverticula, as we have seen, contain carbonic-acid gas, and it is to this constituent that Schaudinn is inclined to attribute the fact that the blood does not clot at the site of puncture; experimental proof of this requires still to be obtained. To what constituent must we attribute the irritation, if it is not due to the saliva? Schaudinn was able to show that it is due to the bacteria contained in the diverticula. He isolated the diverticula, pressed out the carbonic-acid gas, and then transferred them on the point of a needle to a minute scratch made in the skin, rubbing them well in. At once the characteristic irritative effect of a mosquito-bite was experienced, accompanied by redness. The effect was indeed more marked than in the case of the mosquito, and lasted longer, and in one experiment, where he used the contents of a diverticulum filled with the bacteria, a thick and painful swelling an inch in diameter was produced, which lasted a week. Schaudinn then attributes the irritation of the mosquito's puncture to the enzymes of these commensual "molds," which, he says, are always present in the mosquito in all stages of its life-history—egg, larva, nympha, imago. This most interesting discovery will, of course, require much further work devoted to it; at present, however, he considers that these "fungi" belong to the *Mycetæ*, and possibly are nearly allied to the *Entomophthoreæ*. It is interesting to note that at the end of suction a few only of these commensual molds are found in the diverticula, together with traces of blood. The blood, however, furnishes sufficient sugar for the molds to thrive upon and multiply in adequate supply for the next puncture. The molds that have been ejected may be, as we have seen, sucked up again and find their way into the stomach, and, in fact, here during digestion they produce mycelial forms and very minute fruit organs, which also can be found in the egg. What, finally, are the processes involved in the act of suction? As soon as the stilets have pierced the skin and blood bathes the end of the proboscis, a powerful abdominal contraction occurs, which has the effect, as we have seen, of expelling the carbonic-acid bubbles from the diverticula, and, together with this, the bacterial enzyme and the salivary secretion. The bubbles are then covered with a layer of blood, in which are mixed up the enzyme and the salivary juice. The enzyme produces irritation at the site of puncture, resulting in increased pressure and flow of blood, while the carbonic acid prevents coagulation of the blood. As soon, now, as the abdominal contraction is ended, a state of negative pressure exists in the cavity of the proboscis and the bubbles, with their covering of blood, molds, and salivary secretion, are sucked up by the capillarity of the tube of the epipharynx. The action of the pump then comes into play, and the contents are passed on into the stomach, aided also by the peristalsis of the esophagus. This peristaltic and pumping action takes place in the interval between two abdominal contractions, and is repeated four or five times, so that the spacious esophagus, the crop, and the diverticula become completely filled. Then ensues another abdominal contraction: the pump returns to its normal position, the valve between the esophagus and pharynx closes, and the blood is forced on into the midgut by the pressure of the abdominal contraction. During this passage, as we have seen, the crop is expanded and filled with blood, and the esophageal valve is opened, so that the flow into the midgut is unimpeded. Often this process proceeds so rapidly and effectively that it is a common sight, in feeding experiments with the *Anophelinæ*, to see the blood ejected from the anus of the mosquito in considerable splashes on the sides of the vessel in which they are kept.

The Digestive Process.—The imbibed mass of blood is surrounded in the crop with a "gelatinous" secretion from the chitin layer, so that the digestion of the blood and the absorption of nutriment take place through this as an intermediary agent. Shortly after the blood has reached the stomach the serum separates from the corpuscles and is found occupying the anterior portion of the cavity, while the corpuscles occupy the posterior dilated portion. The corpuscles are then acted upon. Hemoglobin dissolves out, and the serum becomes tinged with it, and finally the corpuscles also are completely broken down. The insoluble residue appears as a mass of brownish-black, highly refractile granules; these are gradually passed on and become mixed with the excretory products of the Malpighian tubes, which consist of crystalline, colorless, refractile granules. As these mix with the undigested products of the blood the contents of the gut change from dark brown to grayish yellow, and when digestion is complete to white, so that by observing the color of the feces deposited by the mosquito, the state of the digestive process can be known; this can be, however, readily ascertained by observation of the stomach with the naked eye. When the excreta have been got rid of completely, the stomach is quite free from its central little black clump at the posterior end. The whole process of digestion is dependent upon the temperature. At a temperature of about 80° F. it is complete in about two days, while at 45° F. it may take as long as eight days. When digestion is complete, regeneration of the epithelium of the digestive tract proceeds, commencing in the fore-gut and invaginated proventriculus. Here cells showing mitotic change can be found, even while in the end of the midgut the epithelium is still undergoing desquamation.

The Vascular System of the Mosquito.—This is not well developed, and the elements which compose it are extremely delicate and difficult to define. The only vessels that exist as definite closed tubes are the large dorsal vessel or heart and its anterior prolongation, the aorta. This dorsal vessel is situated just below the abdominal tergal plates. It is suspended by a number of muscular fibers running in pairs from the side of each abdominal segment, giving the dorsal vessel a festooned appearance. Internally the heart is lined with a homogeneous layer in which a number of flat nuclei are distributed. The wall, which is extremely thin, consists of a few muscular threads. Externally there lie on it the so-called pericardial cells. These cells, the largest in the body, are granular, opaque-looking cells, containing some yellowish pigment and one or more nuclei. They can be followed back as far as the rectum, while the dorsal vessel appears to end about the level of the colon. Anteriorly the heart is continued forward as the aorta, passing beneath the mesophragma. In the thorax it gives off four branches, two of which supply the salivary glands, losing themselves in sinuses in that structure, while two other branches follow the course of the esophagus. The main aorta passes on through the neck and is distributed to the head. The aorta can easily be seen pulsating in the living mosquito. For this purpose it is best to use an old mosquito which has lost a good many of its scales. With a strong illumination under the microscope the heart can be seen to contract, according to Schaudinn, four or five times consecutively; then follows a pause of about three seconds. It is during this interval that the respiratory process effected by the contraction of the abdomen goes on, and then follows the peristaltic wave, which can be observed passing from before backward over the ileum.

Fat-Body.—Fat is disposed in the body in two different ways: (1) As a general lining to the body-wall lying immediately below the cuticle; (2) as isolated lobular masses in connection with the various organs and the muscles. Thus we find a lobe of the fat-body in close association with the salivary glands.

Histology.—The cells composing the fat-body are of considerable size and contain numerous oil-globules, with some granular material and also minute dark, refractile granules suggesting pigment. The cells contain deeply staining oval nuclei. The "pigment" granules are most abundant in old mosquitos.

The Muscular System.—The main mass of muscle in the mosquito occupies the thorax. Here two large bands pass on either side dorsoventrally, while between these lateral masses bands running in an anteroposterior direction occur. Neither of these masses is inserted directly into the wings, the movement of the latter being effected by alterations in shape in the thorax due to contractions of the vertical and horizontal systems. We have already noticed the band of muscle which passes outside the salivary glands on either side, and which probably serves to exert pressure on these and so promote the flow of the fluid in the intra-acinar lumen. In the head we have already described the muscles that serve to work the pharyngeal pump. We have, further, various longitudinal bands which serve to move the various portions of the proboscis.

(1) *The mandibles* are at their base attached to a fine tendon connected with a muscle arising from the ventral surface of the exoskeleton of the head, at the point where it is folded in beneath the eyes. The muscle runs forward and downward.

(2) *The maxillæ* appear to arise from the under surface of the maxillary palpi, between them and the upper surface of the labrum. From this point, however, they are continued back as thick, chitinous apodemes or rods to the back of the head, where they end in stumpy processes apparently lying free in the cellular tissue; three sets of muscles act upon this intracranial apodeme of the maxillæ: (*a*) A horizontal muscle, attached along the outer margin for the greater part of its length: this muscle arises from the lower occipital region; (*b*) a muscle inserted along the ventral side of the rod and taking its origin from the base of the labrum; (*c*) a muscle arising from the dorsal surface and inserted into the first joint of the maxillary palpi.

(3) *The labrum* ends in the *clypeus,* but is continued upward as a chitinous rod to which is attached a fan-shaped muscle taking its origin from the exoskeleton of the clypeus.

(4) *The hypopharynx,* the muscular apparatus of the salivary receptacle, has already been described.

(5) *The Labium.*—Attached to its basal portion are a pair of spindle-shaped muscles; they arise from the under surface of the chitinous prolongations of the maxillæ in the cranium, and are inserted into the groove which separates the labium from the under surface of the head.

(6) *The Labellæ.*—The muscles supplying these mobile appendages at the end of the labium arise from the chitinous projections from the inner surface of the labium. They unite to form a common tendon, and are inserted into a chitinous rod which exists at the base of the labellæ. By the contraction of these muscles the labellæ are opened and rotated so that their inner surfaces look downward.

Abdominal Muscles.—These are longitudinal and ventral; the former pass from one segment to the next; they form a dorsal and a ventral lateral group. The ventral muscles pass from the dorsum to the ventral side. By their contraction they flatten the abdomen.

The Tracheal System.—The tracheæ, which supply in their finest ramifications the whole of the tissues of the mosquito with air, take their origin in spiracles situated on the surface of the body. There are two thoracic spiracles—one in the mesothoracic and the other in the metathoracic segment. In the abdomen there are spiracles in the pleural membrane of each segment. From the main thoracic spiracle, which is the largest in the body, several branches pass off: (1) A large branch to the head and neck; before entering the neck it gives off a branch to the salivary glands; (2) a branch passing backward and upward supplying the wing muscles; (3) a branch passing backward and downward, from which numerous secondary branches are given off to the thorax; posteriorly it forms a loop with the main anterior branch of the second spiracle. Branches pass off from this loop to supply the fore-gut. Each trachea arising from the abdominal spiracles gives off a dorsal and ventral branch, uniting with their fellows on the opposite side and connected with each other by longitudinal commissures. The midgut is supplied by the fourth and fifth while the genital organs are supplied by the sixth and seventh.

Histology.—The tubes are lined by a single layer of flattened cells limited by a chitinous intima. As the diameter of the tube diminishes, the epithelial cell may embrace almost the whole circumference, the nuclei being curved round. The chitinous layer is thickened in parts, taking the form of a spiral thread. This thread persists until the diameter of the tube reaches about 4 μ. The terminal capillaries lose themselves in the substance of large branched cells which often have a cribriform appearance for this reason. These cells are especially well seen in the ovaries of newly hatched mosquitos.

Nervous System.—The nerve-ganglia of the mosquito are well developed. In the head there are the large supra-esophageal and infra-esophageal ganglia surrounding the horizontal portion of the pharynx. These give off nerves to the eyes, antennæ, and mouth. From the infra-esophageal ganglion pass back two nerve-cords, following the course of the salivary duct, to join the large conjoined thoracic ventral ganglion. From this ganglion the limbs are supplied with nerves, and posteriorly it is connected with the chain of abdominal ganglia lying close upon the abdominal sterna. Besides these main ganglia there are also ganglia in connection with the viscera, such as those lying beneath the fore-gut and anterior portion of the midgut.

The Reproductive System.—The ovaries and oviduct, the spermathecæ, and accessory glands are comprised in this system in the female. The ovaries are two oval structures lying dorsally to the gut. From these proceed the oviducts, which join below the rectum, forming the common oviduct, which, at first dilated, subsequently narrows. The dilated portion is, according to Kulagin, especially developed at the period of oviposition. It then curves dorsally somewhat forward, and, pursuing a sinuous course, opens beneath the anal opening. At about the point where the oviduct opens into the genital canal open also the ducts (four in *Culex*, two in *Anopheles*) of accessory organs, to be described later on. The ovaries in the newly hatched mosquito lie in the fourth and fifth abdominal segments, but they soon enlarge, so as to occupy the greater part of the posterior portion of the abdomen. The size of the ovaries varies from ½ to 1 mm. in autumn and winter, to 1½ mm. in spring, when there is an accompanying growth of the eggs. The ovaries are surrounded by a sheath of connective tissue in which the tracheæ are embedded. The ovary proper consists of a number of follicular tubes containing the egg-follicles. These tubes are radially arranged around a central tube, which is continuous with the oviduct. Each tube is covered with a thin membrana propria, best seen, as pointed out by Kulagin, in fresh specimens teased out in salt solution, and this membrane is, in fact, a prolongation inward of the general peritoneal covering of the ovary. The egg-follicles which fill the follicular tubes vary in structure according to their state of development. In a follicle of medium development we find externally the cubical follicular epithelium, while in the interior we have cells of two kinds: at the proximal end, cells which serve to nourish the egg,—the "nurse" cells,—while at the end of the follicle nearest the tube are the egg-cells. The number of these nurse cells is three or four. As development proceeds they are absorbed into the ovum, and when the egg is ripe, they have completely disappeared. The follicular epithelium becomes flattened, and forms eventually the chorion of the egg (Christophers). The outer portion of the layer (exochorion) is furnished with oblique parallel markings. The micropylar apparatus is situated at the proximal end, and consists of a globular mass ornamented with rows of pits (Christophers). The oviduct consists of an outer layer in which nuclei are embedded, and a number of muscular fibers; beneath this lies a single layer of flat cells. The portion of this duct beyond the junction of the two oviducts and beyond the dilated portion is the vagina. The epithelial lining is here more highly developed and is cubical in character. Further, the vaginal tube is at this point provided with a thick chitinous coat, an extension inward of the external chitinous integument. Over the opening of the vagina project two flap-like processes which are used in the deposition of ova. The accessory glands and ducts in connection with the vagina are four in number (two in *Anopheles*). Three of these structures are spheric in shape and have a brownish-black, chitinous appearance, while the fourth is oblong or claviform in appearance and is glandular in structure. The spheric bodies are the *receptacula seminis* or *spermathecæ*, for in the fertilized female the contents of these are found to be spermatozoa, while the function of the gland is supposed to be to supply the cement substance, which, in the case of *Culex*, serves to bind the eggs together. The gland itself is composed of cylindric epithelium with the nuclei of the cells almost abutting on the lumen. As we have already pointed out, the egg-cells may be almost entirely destroyed by an invasion of *Sporozoa*.

The Occurrence of Flukes in the Anophelinæ.—Martirano and Schoo and Ruge have noted the occurrence of flukes in the *Anophelinæ*. Thus Martirano found that in May, 1 to 20 per cent., but in June, 50 per cent., of *A. maculipennis* contained encysted flukes. These were found free in the stomach and esophagus, and also in the walls of the former and apparently also in the salivary gland.

They were actively motile, and when pressed out of the cysts, they measured 1.3 mm. long by 0.3 mm. wide. Two suckers and the genital organs were observed. Schoo in Holland and Ruge in Germany have confirmed this, and by Christophers and myself flukes have also been observed in dissections of West African *Anophelinæ*. It is probable that more than one species of fluke will be found. Whether these flukes are human or avian, as suggested by Dr. Brandes, remains to be seen, and it remains to be found out whether the larval stages of these flukes are passed in the larva and nympha of the mosquito and what their further life-history in the mosquito itself is.

Occurrence of Sporozoa in Anophelinæ.—We have noticed the occurrence, in the ova, of *Sporozoa*, and Grassi also describes such and others in the body-cavity. We should mention here the parasites described by American authors in the esophageal diverticulum, etc., of *Stegomyia*, which probably belong to the genus *Nosema*. They are a common occurrence in this genus.

Occurrence of Gregarines in Anophelinæ.—Johnson, in Massachusetts, records the finding of gregarines in *A. maculipennis*. They were found on the outer surface of the "stomach"; also on the Malpighian tubes, and even in the salivary gland; they varied in size from 12 to 80 μ. They are said to resemble malarial oöcysts in appearance. Gregarines also occur in the gut of larvæ.

Occurrence of Flagellata in Anophelinæ.—They are not uncommonly met with in the gut (hind-gut especially). Leger has described the developmental stages of a flagellate which he has called *Crithidia fasciculata;* at first like a grain of corn in appearance, it develops into a trypanosome-like body. It is possibly a developmental stage in the mosquito of some protozoön.

Bacillary Infection of Anophelinæ.—Perroncito describes an organism resembling *Leptothrix buccalis*, which he considers to be pathogenic to the mosquito.

Ectoparasites of Anophelinæ, etc.—They occur on *Anophelinæ*, but also on other *Culicidæ*. They are *Acarinæ*, among which have been identified *Tyroglyphus siro*, *Chryletas eruditus*, *Gamasus sp.*, and hexapod larvæ of *Hydrachnidæ*, some of these belonging to the genera *Hydrodroma* or *Nesæa*.

External Anatomy.—The head is composed mainly of the two large compound eyes, which, dorsally, are separated by an area bearing a tuft of hairs (in *Anopheles*), but ventrally they are separated only by a narrow line. Looking at the head from in front, we see that in the space between the eyes are the large, swollen basal joints of the antennæ, and below these the centrally placed prolongation forward, the *clypeus*, with the labrum epipharynx; and below it again the labium. The head is joined to the neck by a membranous neck in which lateral chitinous plates occur. The portion of the head lying behind the eyes is the *occiput*, while behind this it is termed the nape, or cervix. The space between the eyes and antennæ is the frons, while the part connecting this with the occiput behind is the vertex; that part of the head that lies beneath the eyes on either side is the gena.

The antennæ arise from the frons. They consist of 15 segments in *A. maculipennis:* the first segment is extremely small; the second globular, and contains a complicated auditory organ; then follows the third segment, which is larger than any of the others. From the proximal end of each segment arise a number of hairs arranged symmetrically around the segment. In the male there are 16 segments. On the fourth to the fifteenth segments occurs that arrangement of long hairs in whorls which gives the male antennæ their characteristic plumose appearance. These whorls are 12 in number. They arise from the antennæ in two half-rings, each consisting of about 30 hairs.

Tubular Passages.—Passing through the head (of *A. maculipennis*) are two tubes, which open by a slit-like trumpet orifice anteriorly between the margin of the eye and the side of the clypeus; posteriorly they open below the origin of the neck near the ventral border. They are probably hollow apodemes, serving for the attachment of muscles. The head is connected with the thorax by a thin neck, which bears laterally two chitinous plates. These approach each other dorsally, and ventrally each sends out a process to meet but not to join each other. The posterior ventral portion of the neck lying in front of the prosterna is thin, permitting one to see the blood passing through it.

The thorax consists of three parts: *prothorax, mesothorax,* and *metathorax.* The main part of the dorsal surface of the mesothorax constitutes the *scutum.* Behind this there is a well-marked ridge, constituting the *scutellum.* Behind this is a triangular, shield-like portion, curved on its upper surface, the *postscutellum,* extending backward as far as the first abdominal segment. We have already referred to its importance in classification from the characters of the hairs or scales found on it or from the absence of any covering. Whether any of the metathorax appears dorsally is doubtful. A small sclerite, however, appears to exist posterior to the postscutellum, between it and the first abdominal segment. Similarly the prothorax is not represented dorsally. The homologies of the parts constituting the thorax are a matter of considerable dispute. It will suffice here to note the structures known as the *patagia*. They are situated on either side of the base of the neck. They limit, laterally, the thin ventral area of the neck. They are sausage-shaped bodies, situated on a pair of freely movable sclerites. These sclerites are continued backward as rod-shaped bodies almost as far as the main thoracic spiracle. Posteriorly this area is bounded by the origin of the first pair of legs (prothoracic). Nothing is known certainly as to the function of the patagia. The episternum and mesosternum form the main lateral surface of the thorax; the wings arise between the scutum and the episternum; the mesosternum also bears a trilobed process, with which the wing articulates when drawn forward. From the episternum of the metathorax arise the halteres or balancers, the homologues of a second pair of wings. Here also is situated the second thoracic spiracle.

The legs are respectively prothoracic, mesothoracic, and metathoracic in origin. They are six in number, and each consists of coxa, trochanter, femur, tibia, and a tarsus consisting of five segments; the first tarsal segment is often termed the metatarsus. The terminal segment of the tarsus bears one or more claws, which may have one or more teeth; the characters of the male ungues are occasionally of help in differentiating mosquitos otherwise similar in appearance. There may be pulvilli, and an empodium between the claws in some forms. The coxa is about twice the length of the trochanter. The length of the metatarsus or first tarsal segment is of specific value in regard to its proportionate length to the tibia in the hind legs of some species.

The abdomen consists of eight segments; each segment consists of a dorsal chitinous plate, the *tergum*, united by the pleural membrane to the ventral plate or sternum. The pleural membrane is pierced by the openings of the abdominal spiracles, though, according to some observers, only six openings can be made out, while others describe eight. They are best seen in the newly hatched insect.

The Genitalia.—On the posterior end of the last segment in the male is a pair of lobed appendages, each terminating in a well-marked claw or clasper, the clasper of one side crossing that of the other. In the female there are no claspers, but from the last segment project two flap-like processes which are probably used for oviposition. The character of the male genitalia is of some importance in classification.

The Wings.—The main features of the wing that are of importance are the arrangement of the veins and the disposition and character of the scales. Though no two nomenclatures of a wing of a *Dipteron* seem to agree, we have adopted one here which at least can readily be followed: (1) *The costal vein* runs along the anterior margin or costa of the wing. (2) The subcostal (or auxiliary or mediastinal) joins the costal at a variable distance from the apex of the wing. (3) *The first longitudinal,* running a practically straight course from the base of the wing to the apex. (4) *The second longitudinal* commences about the middle of the wing, and after a little distance divides into branches or forks, the space included between the branches being termed a forked cell. This is the *anterior forked cell* (or first submarginal cell). The branches of the second longitudinal vein may be termed anterior and posterior respectively. (5) *The third longitudinal* vein, arising from near the middle of the wing but nearer the apex than the second, runs straight to the margin. (6) *The fourth longitudinal* vein commences at the base of the wing and is also branched near the extremity, forming the *first posterior* forked cell. (7) *The fifth longitudinal* vein arises also from the base, and, running a sloping course, gives off a large anterior branch inclosing the *second posterior forked cell.* (8) *The sixth longitudinal* vein runs a sinuous course and is not branched. In the *Heptaphlebomyina* there is a seventh longitudinal vein. Besides these longitudinal veins there are several cross veins, three of which are situated at the base, joining the costal and subcostal; first and third longitudinal, third and fifth longitudinal respectively. There is also a cross vein joining the second longitudinal at its margin with the first longitudinal in front. Neither of these veins is of as much importance as the three following, which vary in position in different species and are of some use in classification, but, owing to their variability in the same species, they must be used with great caution. They are situated about the middle of the wing field, and are known respectively as—(1) The *anterior* or *supernumerary* cross vein; it connects the third at its origin with the second in front; (2) the *midcross vein,* joining the third at its origin with the fourth posteriorly; and (3) the *posterior cross vein,* joining the branch of the fifth cross vein with the fourth in front. With regard to the fork cells, we may give as examples of the variations found in them: (1) In the *Anophelinæ* the anterior forked cell is as long or longer than the first posterior forked cell; (2) in the *Megarhininæ* it is very small and much smaller than the first posterior forked cell; (3) in the *Culicinæ* it is as long or longer than the posterior forked cell; (4) in the *Aedeomyinæ* the forked cells are very small and the anterior is smaller than the posterior. Again, the position of the cross veins varies in different genera; thus in *Hæmagogus* the posterior cross vein is nearer the base than the mid, whereas in *Sabethes* it is nearer the apex, but these differences are of minor importance compared with scale structure.

In the classification of the *Culicidæ* the structure of the scales of the different parts of the body, especially those of the head, thorax, and wings, is of the greatest importance, and a knowledge of these, which is readily obtained, will greatly simplify the identification of a particular mosquito, or at least assigning it to its proper genus. The determination of the species can be done only by reference to a systematic treatise, *e. g.*, Theobald's "Monograph of the *Culicidæ* of the World."

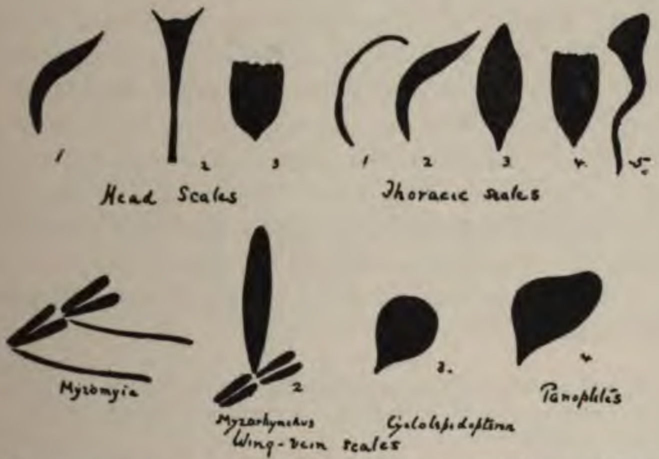

FIG. 6.—VARIETIES OF SCALES (after Theobald) (from Stephens and Christophers' "Practical Study of Malaria").

A. Head Scales.—These are of three types: (1) Narrow curved scales; (2) upright forked scales, situated usually posteriorly; and (3) flat scales, closely applied to the head like the tiles on a roof. These three varieties can readily be recognized.

B. Thoracic Scales.—These may be of several types, of which the following are most common: (1) Hair-like curved scales; these are finer than narrow-curved scales and may form a dense felt-work over the mesothorax. (2) Narrow curved scales; these may occur over all the mesothorax and scutellum. (3) Spindle-shaped scales;

they lie scattered about and do not form a complete covering. (4) Flat scales, like those on the head. They occur, for instance, on the scutellum, in the genus *Stegomyia*. (5) Long twisted scales expanded at the end in the genus *Mucidus*.

C. Abdominal Scales.—These, in the vast majority of the *Culicidæ*, are flat scales. In the *Anophelinæ*, except in the genus *Aldrichia*, they are, however, almost entirely absent.

D. Wing Scales.—The veins (except the cross veins) have—(1) flat scales, arranged in a double row along each vein, while generally there are also (2) lateral scales along each vein. These vary much in shape, and may be—(1) Broad, asymmetric, flat scales—*e. g.*, in *Mansonia* and *Aedeomyia;* (2) pyriform particolored scales, half dark, half white—*e. g.*, in *Mucidus;* (3) large inflated scales, as in *Cyclolepidopteron;* (4) in general, lanceolate or long and narrow.

E. Wing Fringe.—These consist of three sets: (1) Border scales—small flat scales; (2) long lanceolate scales projecting from the border; (3) shorter lanceolate scales lying between No. 2.

F. Leg Scales.—These are for the most part flat scales—(1) In *Sabethes* they are hair-like and occur in tufts or paddles; (2) in *Mucidus*, *Psorophora*, etc., they are elongated and project from the legs. The division of the *Culicidæ* into subfamilies is based mainly on the length of the palpi in the male and female, together with the absence or presence of scales or hairs on certain parts. We have the following 7 subfamilies:

1. Palpi long in both sexes, as long as the proboscis in the female ...... *Anophelina*.
2. Palpi long in both sexes, nearly as long as or rather shorter than the proboscis in the female ...... *Megarhinina*.
3. Palpi long in male, short in female ...... *Culicina*.
4. Palpi long in male, short in female, postscutellum with hairs and scales. . *Joblotina*.
5. Seven longitudinal veins (not six) ...... *Heptaphlebomyina*.
6. Palpi very short in female and male ...... *Aedeomyina*.
7. Proboscis short, not formed for piercing ...... *Corethrina*.

CLASSIFICATION OF CULICIDAE.*

Subfamily *Megarhininæ*.—Palpi about as long as proboscis in male, nearly as long as proboscis or rather shorter in female. First forked cell very small—smaller than the first posterior forked cell.

GENUS 1: *Megarhinus:* Palpi, 5 segments in male and female, proboscis bent, characterized—(1) By their large size (elephant mosquitos); (2) their brilliant metallic colors; (3) the caudal tuft of hairs on each side of the abdomen; (4) head clothed with flat scales only. Species six.

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* Mr. F. V. Theobald, author of "A Monograph of the *Culicidæ* of the World," has very kindly read through the manuscript of this systematic portion.

GENUS 2: *Toxorhynchites:* Easily distinguished from the former by the palpi, 3 segments in ♀, quite short. Species four.

Subfamily *Culicinæ.*—Palpi short in ♀, long in ♂. Anterior forked cell as long or longer than first posterior forked cell. Posterior cross vein usually nearer the base than the midcross vein, but in rare exceptions may be nearer apex (*Theobaldia incidens*).

GENUS 1:.*Janthinosoma:* Easily distinguished from *Culex* by the densely scaled hind legs, giving a characteristic appearance. Hind tarsi white. Palpi densely scaled. Head, flat, broad spindle scales, and some upright forked. A pseudo-vein runs through the first basal cell.

GENUS 2: *Psorophora:* (1) Proboscis bent in ♀; (2) palpi in ♂ very long, 5 segments; (3) densely scaled long legs. Species four.

GENUS 3: *Mucidus:* At once told by their moldy, ragged appearance. (1) Wing scales large, half dark, half white; (2) head and thoracic scales long, twisted, expanded at the apex; (3) legs densely scaled, with projecting scales. Species five.

GENUS 4: *Desvoidea* (syn. *Armigeres*): Head, flat scales only, with a few upright forked. Distinguished from *Stegomyia* by—(1) Unbanded tarsi and abdomen; (2) palpi in ♂ untufted, thin, and acuminate; (3) palpi in ♀ very pointed and clothed with bristles only. Species two.

GENUS 5: *Stegomyia:* (1) Head, flat scales only and a few upright forked; (2) palpi, 4 segments in ♀, 5 in ♂, the segments about equal in length; (3) scutellar scales, flat. Generally black and white mosquitos, with banded legs and abdomen. Very persistent and silent in their attacks. Species twenty. *S. fasciata:* (1) Tarsi *basally* banded white; (2) proboscis unbanded; (3) thorax dark brown, a pure white, broad curved band on each side, curved inward about the middle of the mesonotum, and continued backward to the scutellum as a thinner line; two thin parallel pale lines between the curved ones; two white patches in front near the neck; (4) ungues of ♀ toothed. Transmits yellow fever.

GENUS 6: *Theobaldia:* (1) Palpi in ♂ clubbed as in the *Anophelinæ.* (2) Palpi in ♀ 5 segments, apical one mammilliform. (3) Wings densely scaled and collected into spots, thus forming a "spotted-wings" genus. Species five.

GENUS 7: *Lutzia:* Distinguished from *Theobaldia* by—(1) The palpi in ♀ have 3 segments only; apical joint is not mammilliform. (2) Palpi in ♂ 3 segments, not clubbed. They also form a group of "spotted-wings" mosquitos. Species one.

Genus 8: *Culex:* Distinguished from *Stegomyia* by the head scales, which are mainly narrow curved, with upright forked scales posteriorly and flat scales only laterally. Palpi in ♀ 3 segments, third segment as long or longer than the other two. Scutellum, narrow curved or spindle scales. *C. mimeticus* has spotted wings. Species very numerous.

Genus 9: *Gilesia:* Resembles *Culex* and *Stegomyia;* distinguished by—(1) Scutellum has small flat scales, a few spindle scales; (2) head, broad flat spindle scales; (3) basal joint of antennæ hairy and scaly; (4) claws short and thick, with a blunt tooth; (5) wing scales like those of *Tæniorhynchus*. Species one.

Genus 10: *Lasioconops:* (1) Head, scales as in *Culex;* (2) basal joint of antennæ a few scales; (3) abdomen has large, projecting, flat scales with deeply dentate apices, giving a ragged appearance. Species one.

Genus 11: *Melanoconion:* Distinguished from *Culex* by the dense broad scales on the costa and apex of the wing, and by the black, spine-like scales along the upper border. Small dark mosquitos. Species six.

Genus 12: *Grabhamia:* Allied to *Culex* and *Tæniorhynchus*. Palpi in ♀ 4 segments. Apical segment minute. Penultimate segments long and thick. Wing scales not so long or dense as in *Tæniorhynchus*. Wing scales mottled. Wings short and stumpy. Legs mottled and spotted. Species ten.

Genus 13: *Acartomyia:* Allied to *Culex* and *Grabhamia*. Distinguished from *Grabhamia* by the flat, irregularly disposed scales all over the head; from *Culex*, by the palpi in the ♂; the two terminal segments and the apex of the antipenultimate swollen. Terminal segment club-shaped. Ragged appearance of head well marked. Species one.

Genus 14: *Tæniorhynchus:* Palpi have 5 segments in the ♂, the fifth minute. Characterized by the wing scales, thick, elongated scales ending with a broad sloping convexity or blunt point. Median linear vein scales often absent. Proboscis generally banded. Species about sixteen.

Genus 15: *Mansonia* (syn. *Panoplites*): Palpi 4 segments in ♂, longer than one-third the proboscis. Characterized by the dense wing scales, broad and asymmetric. No median scales; resembles

Aedeomyia, but the short palpi in the male of the latter distinguish it. Species eight.

GENUS 16: *Katageiomyia:* Head, irregular flat scales, a few narrow curved on nape, also numerous upright forked. Palpi short in the ♀, 3 segments, the last as long as the two basal ones. Palpi in ♂ long, but not nearly so long as proboscis. Thorax narrow, curved scales. Midlobe of scutellum, small flat scales, narrow curved on lateral lobes. Differs from *Stegomyia* in—(1) Having narrow curved scales on back of head; (2) narrow curved scales on lateral lobes of scutellum.

GENUS 17: *Macleaya:* Resembles closely *Stegomyia*, but differs in having—(1) Narrow curved scales on the center of the head and (2) on the lateral lobes of the scutellum. Species one.

GENUS 18: *Hodgesia* (probably an *Aedeomyina*); Palpi in ♀ very short, apparently one-jointed. Head clothed with flat scales. Resembles superficially *Stegomyia*. Characterized by the lateral vein scales on the wing. They are long and nearly overlap those of contiguous veins. The apices of the scales have marked lateral spines. Species one.

GENUS 19: *Scutomyia:* Differs from *Stegomyia* in having narrow curved scales on head, and from *Macleaya* in having the scutellum entirely clothed with flat scales. From *Leicesteria* it differs in having all scutellar scales flat. Species one—Malay.

GENUS 20: *Danielsia:* Distinguished from *Macleaya* and *Scutomyia* by the narrow, curved scutellar scales and from *Katageiomyia* by the long male palpi. Species one—Malay.

GENUS 21: *Eretmapodites:* Head, flat and upright forked scales. Scutellum with flat scales on midlobe. Palpi in ♀ four-jointed, in ♂ five-jointed, long, thin, and hairless. Last two hind tarsi in ♂ densely scaled, forming a paddle in one species. Wing scales long and rather thick. Species two.

GENUS 22: *Finlaya:* Three ventral abdominal scale tufts. Scutellum four median bristles. Wing scales large, broad, and pyriform. Species two.

GENUS 23: *Howardina:* Palpi 4 segments, apical one minute, not mammilliform; resembles *Ædes*. Scutellum 4 bristles.

GENUS 24: *Skusea:* Head, flat scales only, anterior and posterior forked cells densely scaled. Palpi in ♀ 3 segments. Scutellum 6 bristles and narrow curved scales. Species three.

GENUS 25: *Hulecoetomyir:* Head, flat scales, with a marked median area of narrow curved scales. Scutellum, with a roset of flat and somewhat spindle-shaped scales on midlobe. Scutellar scales rounded apically. Distinguished from *Stegomyia* by the head and scutellar scales.

GENUS 26: *Leicesteria* (unpublished).

Subfamily *Joblotinæ* (Syn. *Trichoprosopinæ*).—GENUS 1: *Joblotia:* Postscutellum (metanotum), with a tuft of chætæ and with flat scales. Clypeus and base of antennæ bristly. Second long vein carried nearly to the base of the wing. Second posterior forked cell very large; wing densely scaled, but the scales are shorter than those of *Tæniorhynchus*. Species one.

Subfamily *Heptaphlebomyinæ*.—GENUS 1: *Heptaphlebomyia:* Distinguished from *Culex* by the presence of the seventh long vein. Species one.

Subfamily *Aedeomyinæ:* Palpi very short in both sexes—much shorter than the proboscis.

GENUS 1: *Deinocerites* (syn. *Brachiomyia*): Characterized by antennæ in ♀ much longer than the proboscis. Second segment as long as the 3 terminal segments. Antennæ scaled. Antennæ pilose in ♂ and longer than the whole body. Species two.

GENUS 2: *Aedes:* The narrow curved scales on the head form a broad median band only, the other scales flat. Scutellum, narrow curved scales and 6 bristles. Palpi in ♀ 4 segments. Apical joint minute and mammilliform. There is a trace of a fifth segment. Species two.

GENUS 3: *Aedimorphus* (probably a *Culicine*): Head, chiefly flat scales, narrow curved behind. Scutellum, flat scales and 8 (?) bristles. No flat thoracic scales, as in *Uranotænia*. Species one.

GENUS 4: *Verrallina* (probably a *Culicine*): Head, as in *Skusea*. Palpi, 2 segments (trace of a third), apical segment large. Scutellum, narrow curved scales and 4 bristles. Species three.

GENUS 5: *Ficalbia:* Head scales, almost all flat, no narrow curved scales. Distinguished from *Uranotænia* by thoracic scales being narrow curved ones. Scutellum, flat scales. Palpi, 2 segments. Species two.

GENUS 6: *Uranotænia* (probably a *Culicine*): Head, flat scales; upright forked scales may or may not be present. Scutellum flat scales. Thorax narrow curved and flat scales. Forked cells small, anterior smaller than posterior. Metallic scales at base of the wings. Brilliant metallic mosquitos, stouter than *Ædes*. Species fourteen.

GENUS 7: *Mimomyia:* Resembles *Uranotænia*. No flat scutellar or thoracic scales. Forked cells larger than in *Uranotænia*. No metallic scales at base of the wings. Species two.

GENUS 8: *Aedeomyia:* Distinguished from *Ædes* by—(1) Head scales upright, fan-shaped; clypeus scaly; (2) thorax, broad, flat spindle scales; (3) scutellum, broad flat scales; (4) legs densely scaled; (5) wings densely scaled, as in *Mansonia;* also with long lateral scales. Species three.

GENUS 9: *Hæmagogus:* Distinguished from *Ædes* by the palpi having 5 segments in both sexes. Head covered with flat scales; brilliant metallic (blue) mosquitos. Species two.

GENUS 10: *Wyeomyia:* Has chætæ on postscutellum (metanotum). Head, flat scales; thorax, spindle and flat scales; scutellum, flat scales; palpi short, proboscis not so long as whole body. Species two.

GENUS 11: *Phoniomyia:* Distinguished from *Wyeomyia*—(1) By wing scales, as in *Tæniorhynchus;* (2) proboscis longer than the whole body. Species two.

GENUS 12: *Dendromyia:* Distinguished from *Wyeomyia* by—(1) Scutellar scales, small, flat, rounded apically; (2) wings more densely scaled than in *Phoniomyia;* (3) proboscis moderately long. Species five.

GENUS 13: *Runchomyia:* Characterized—(1) By frons projecting as a blunt spine; (2) proboscis as long as the body in the ♀; (3) ventral apical tuft of bristles; (4) wing scales, rather broad, species one.

GENUS 14: *Sabethes:* Distinguished from *Wyeomyia* by the asymmetric wing scales. One or more legs with dense, paddle-like structures in both sexes. Third long vein carried through into the basal cell. Posterior cross vein nearer the apex than the mid in the ♂. Brilliant metallic mosquitos. Species four.

GENUS 15: *Sabethoides:* Distinguished from *Sabethes*—(1) By smaller palpi; (2) unpaddled legs. Species one.

GENUS 16: *Goeldia:* Postscutellum (metanotum) has chætæ and scales; wing scales dense, elongated, as in *Runchomyia;* proboscis short and thick; not as long as body; palpi in ♂ one-third the length of the proboscis; in ♀ quite short. Species one.

GENUS 17: *Limatus:* Characterized by its proboscis bent in the middle, densely scaled at the bend. Species one.

CLASSIFICATION OF THE ANOPHELINAE.

The old genus *Anopheles* has been divided by Theobald into 12 new genera. The basis of this classification is almost entirely dependent on scale structure.

1. *Anopheles.*—Thorax and abdomen have hair-like, curved scales. Palpi not densely scaled; lateral scales of wing veins long and lanceolate. Spots on the wing few, or absent in some species.

2. *Myzomyia.*—Thorax and abdomen with hair-like, curved scales. There may be a tuft of narrow curved scales in front of the thorax, projecting forward. Wings spotted and distinguished from those of the genus *Anopheles* by little beyond the shape of the lateral scales of the wing veins, which are long thin scales, but narrow lanceolate also occur. They are very often small dark mosquitos.

3. *Cyclolepidopteron.*—Thorax and abdomen with narrow, curved, almost hair-like scales. Head covered with upright forked scales. Easily distinguished from the two previous genera by the wing scales. Besides the lanceolate scales, there are characteristic large inflated scales.

4. *Stethomyia.* — Thorax bristly, apparently nude, prothoracic lobes mammillated and bearing bristles. Abdomen very hairy—large and small hairs. Wings unspotted; the veins have long lanceolate scales. Easily distinguished from *Anopheles* by its mammillated prothoracic lobes and by the presence of some flat scales on the head, which are not found in *Anopheles.*

5. *Pyretophorus.*—Thorax with narrow curved scales; abdomen, hair-like scales; wings distinctly spotted. Scales of wing veins, narrow or lanceolate. Palpi; fair amount of scales. Legs generally banded or even spotted. Distinguished from *Myzomyia* by its thoracic scales. Has no flat scales on the head.

6. *Arribalzagia.*—Thorax with hair-like scales and some narrow curved; abdomen has large apical lateral scale-tufts. Palpi densely scaled. Legs banded and speckled. Closely related to the next genus.

7. *Myzorhynchus.*—Thorax, hair-like scales. Abdomen no lateral scale tufts, but a ventral apical tuft. Palpi densely scaled, distinguished from the former by the absence of the lateral scale tufts.

8. *Christya.*—Thorax with hair-like scales and narrow curved lateral ones; abdomen with dense long lateral apical tufts of hair-like scales (characteristic). Wings dense lanceolate scales.

9. *Nyssorhynchus.*—Thorax has narrow curved and spindle-shaped scales, abdominal scales variable in character and quantity; sometimes ventral, sometimes on the apical segment only, sometimes with dorsal apical patches. Palpi densely scaled. Wing scales lanceolate.

10. *Cellia.*—Thorax, flat spindle scales. Abdominal scales differ from those of *Nyssorhynchus* by the fact that they almost completely

cover the abdomen. The scales are narrow curved or spindle, with dense lateral tufts. Palpi densely scaled. Wings densely scaled, with blunt lanceolate scales, differing from those of *Nyssorhynchus*.

11. *Aldrichia.*—Thorax, hair-like scales. Prothoracic lobes have projecting flat scales. Characterized by the abdomen being covered with flat scales, as in *Culex*.

12. *Genus Lophoscelomyia.*—Resembles *Nyssorhynchus*, but differs from it in having—(1) Long, curved, hair-like scales on the thorax instead of narrow, curved, and spindle-shaped ones; (2) marked dense apical tufts on the hind femora in both sexes.

Differentiation of Species.—Some of the *Anophelinæ* can be readily told by merely examining the wing or the banding on a leg, though it should be remembered that a too hasty examination is apt to lead one to overlook new species and even genera. The main features that are of use are—(1) The wings: (*a*) The main spots of the wing are formed by collections of scales on the costal, subcostal, and first longitudinal veins; these sometimes exhibit characteristic arrangements—*e. g.*, the T spot in *M. rossii* or the interrupted spot of *P. costalis*. It should be recognized that variations occur in these spots, and that they are by no means constant, so that small differences do not suffice to create a new variety, much less a species. This may be seen in a number of *Anophelinæ* bred out from the same batch of eggs, but the number and arrangement of the spots are, all the same, of great use in distinguishing species. (*b*) Besides the main costal spots, the small areas of scales on the third to the sixth long veins are of use, and in an accurate description of a wing each of these areas should be marked. Thus *M. leucosphyrus* has six spots on the sixth long vein, while *M. elegans* has only four. (*c*) The extent to which the third longitudinal vein is scaled is also of specific importance. (*d*) Finally the wing fringe has at the points where the longitudinal veins cut the margin a variable number of pale areas. Thus *A. punctipennis* has only one pale area, while *A. pseudopunctipennis* has several; *M. rhodesiensis* has one small apical fringe spot; *M. funestus*, six spots. (2) The legs: The tarsal segments may be banded or speckled. The banding may be apical or basal on the tarsal segments. Many of the species of the genus *Nyssorhynchus* can be distinguished at once by the number of white tarsal bands, which may vary from one to three and a fraction of the next segment. The femora and tibiæ may be speckled or unspeckled. Similarly in the genus *Cellia*. Most of the species are easily told by simply examining the tarsi of the hind legs. (3) The palpi: Just as in the case of the legs, so by the banding of the palpi formed by collections of white scales great assistance is given in the determination of species. The apices of the palpi are, as a rule, white, but they are dark in *M. rhodesiensis*, *M. hispaniola*, *M. turkhudi*, and in *N. theobaldi var. nagpurensis*. Besides the apical band, the other bands are of great aid—*e. g.*, the number of bands, their distance apart, whether or not the two apical ones are equal in width, and so forth. It should always be remembered, in making minute comparisons, that an observed difference may be found normally in the species, and the occurrence of seasonal variations has also to be considered. Of minor importance are the characters of the male genitalia, the character of the ungues in the male and the position of the cross veins on the wings; this latter is, indeed, of but slight use.

Yet another feature has been used by Dönitz in differentiating species—viz., the shape of the eyes and the shape and width of the portion of the frons intervening between the eyes. The shape of the eyes is determined by counting the columns of facets in the eyes, and the shape of the intra-ocular portion by determining whether the sides of the eyes are parallel or converging; whether they are close together or widely separate. Thus in *A. maculipennis* the number of facets in longitudinal series is 4, 7, 8, 9, 10, 11, etc., and the inner margins of the eyes are parallel. The facets can readily be counted in specimens freshly mounted, but our own experience has been that it very difficult, if not impossible, in old specimens, owing to shrinkage and distortion.

Genus I: *Anopheles:* Larva, clypeal hairs generally branched. The species may be classified as follows: (A) Costa uniform, wings spotted —(1) *A. maculipennis:* Wings, field four spots, apex of first tarsal segment spotted. Europe and North America. Transmits malaria. (2) *A. crucians:* White spots on brown veins; three black spots on sixth vein; tarsi unbanded. North America. (2^A) *A. eiseni:* Resembles *A. maculipennis;* apices of hind tarsi yellowish. Hill species, Guatemala. (B) Costa spotted. (3) *A. punctipennis:* Two yellow spots—one at the apex, the second on the apical third; one fringe spot. North America. (4) *A. pseudopunctipennis:* Wings as in *A. punctipennis*, but wing fringe with several spots. North America. (4^A) *A. punctipennis* (Say. "Var. A," Theobald): Three costal spots. (4^B) *A. franciscanus:* Costa two spots, one apical, pure yellow, the second small, opposite about middle of costa. Wing fringe indistinct spot at all the junctions. Tarsi unbanded. California. (5) *A. gigas:* Costa two large black spots, length 5 to 6 mm. India. (6) *A. lindesayi:*

Costa black, apical white spot. Femora have characteristic broad median white band. Hill species, India. (C) Wings unspotted. (7) *A. bifurcatus:* Thorax with golden hairs arranged so as to leave two broad bare lines on the front part; abdominal hairs golden. ♀ 5 to 5.5 mm., ♂ 6 mm. Transmits malaria (probably = *A. walkeri*). Europe. (8) *A. algeriensis:* Abdominal hairs dull brown. Anterior forked cell shorter than in *A. bifurcatus.* ♀ 3.5 to 4.5 mm., ♂ 5 to 5.5 mm. The lateral scales of the veins are longer and finer than in *A. bifurcatus,* also the anterior and posterior cross-veins are in the same line in both sexes, whereas in *A. bifurcatus* the posterior is internal in the ♀, the anterior is internal in the ♂. (9) *A. nigripes:* A black species. No bands on tarsi. Europe (? North America). (10) *A. immaculatus:* Ash gray in color; slight apical bandings to tarsi. Palpi and proboscis lighter at apex. Madras, India. (11) *A. aitkeni:* Uniformly dark, no bands on palpi or legs. Goa, India. (12) *A. stigmaticus:* Light brown; tarsi unbanded. Australia. (13) *A. annulipalpis:* Tarsi banded; last tarsus pure white. South America.

Genus 2: *Myzomyia:* Clypeal hairs of larvæ simple in those hitherto described.

Group I: Small dark mosquitos, breeding in fresh natural waters, canals, streams, etc. (1) *M. funesta:* Costa with four white spots. Basal portion of costa has also pale interruptions; wing fringe pale spots at the end of all the veins except the sixth. Palpi, three bands; basal one further from the middle one than the apical. A variable species. Third long vein may be dark. Resemble *M. listoni* and *M. rhodesiensis.* Especially active in transmitting malaria in West Africa, etc. (2) *M. listoni:* Third long vein light; wing fringe, four or more light spots. Palpi, two broad apical bands further apart than in *M. funesta.* One narrower basal band. Transmits malaria in India. (3) *M. aconita:* No dark spot at the commencement of the third long vein. Costa four spots; light interruption in basal spot. Differs from *M. listoni* in palpi having four bands. Wing fringe several pale areas. Tarsi banded. Anterior forked cell longer and narrower than posterior. Sumatra, Java. Probably the same as *A. formosaensis I.* (4) *M. culicifacies:* Third longitudinal vein dark; wing fringe, three spots at most. Palpi, three equal bands—two at the joints, one at the apex. Attitude, "culex"-like. Transmits malaria in India. (5) *M. leptomeres:* Base of first long vein white; costa, two yellow spots, apex pale, thus distinguished from *M. hebes.* Wing fringe, pale areas at all the veins. India. (6) *M. hebes:* Resembles *M. rhodesiensis;* wing costa four spots, wing fringe seven light areas. One spot on sixth vein. Palpi first and second segments covered with white scales; end of third segment dark; fourth segment white. Description by recorder incomplete. East Africa.

Group II: Larger mosquitos than those of group I; lighter, wings not so many dark scales. (7) *M. albirostris:* Characterized by the proboscis apically banded with white scales to about half its length; a very small species, 2.5 μ. Malay. (8) *M. longipalpis:* Palpi long, thin, three narrow bands. Wing costa black, four almost equal yellow spots, wings mostly brown scales. Hind legs only banded with narrow basal and apical bands. British Central Africa. (9) *M. ludlowii:* Probably a spotted variety of *M. rossii;* palpi broad apical white band; two other smaller bands; the two distal bands close together. Wing costa, four large spots; one or two small basal spots. Femora, tibiæ, and metatarsi, especially in hind legs, spotted with yellow. Tarsi broad, apical, and basal pale banding, especially in hind legs. Philippine Isles. (10) *M. rossii* (= *A. vagus* Dönitz): Palpi, apical band broader than in *M. ludlowii.* The second large spot on the costa has the characteristic T shape, but varies, even in opposite wings of the same mosquito. Slight apical and basal bands to some of the tarsi. India, Malay, Egypt (?). (11) *M. lutzii:* Characterized by the linear ornamentation on the thorax and five marked bands on the fore and mid- metatarsi. Wing costa three distinct spots, two smaller ones. (12) *M. elegans:* Palpi, four white bands, characterized by a large tibia—metatarsal band on the hind legs. Differs from *M. leucosphyrus* in having four, not six, spots on the sixth vein. Resembles *N. stephensi;* differs in palpi, has four, not three, spots on the sixth vein. (13) *M. tesselatum:* Distal half of proboscis pale, with a narrow black ring near the apex. Costa, four large, four small spots. Fore tarsi basally and apically banded; mid and hind tarsi, apically only. Thorax, two dark spots in front and a dark area near the scutellum. Sixth vein, four spots. Malay. (14) *M. punctulatus:* Only tip of proboscis pale. Costa, four large spots and several small spots. Sixth vein three spots; closely resembles *M. tesselatum,* but has not the thoracic markings. Malay. (15) *M. leucosphyrus:* Proboscis dark; six spots on sixth vein; resembles two previous species, distinguished by prominent tibio-metatarsal band and by the prominent median dark spot on the costa. (16) *M. impunctus:* Costa four small dark spots. Fringe spotted. Sixth vein three spots; veins as a whole but few spots. Doubtful species. Egypt.

Group III: Dark mosquitos, with apex of palpi black. (17) *M. turkhudi:* Palpi apices black, the band not so broad as in *M. hispaniola;* third vein mostly dark, but variable. Pale interruptions in basal costal spot. India. (18) *M. hispaniola:* Third long vein mostly yellow, except at the base and apex. Wing fringe spotted, except opposite the lower branch of the fifth vein and sixth vein. Basal portion of costa uniformly black. Spain. (19) *M. rhodesiensis:* Third long vein dark; palpi, two bands. Palpi longer and thinner than in *M. funesta;* base of the costa black; there is a pale interruption in *M. funesta.* Wing fringe, only an apical spot. Costa three white spots and a yellow apical spot. Rhodesia. (20) *M. vincenti:* Resembles *M. rossii,* but has not the T spot. Has only apical spots to tarsi. Anterior fork cell larger than posterior (position doubtful).

Genus 3: *Cyclolepidopteron:* (1) *Cy. grabhami:* Palpi unbanded. Jamaica. (2) *Cy. mediopunctatus:* Palpi banded, black and gold. Brazil.

Genus 4: *Stethomyia:* (1) *S. nimba:* Wings unspotted; thorax, brilliant silvery, median band and lateral gray bands; palpi longer than proboscis in both sexes. British Guiana, South America. (2) *S. fragilis:* Wings unspotted; thorax greenish brown; proboscis in ♂ longer than palpi. Malay.

Genus 5: *Pyretophorus:* (1) *P. superpictus:* Wing costa four distinct spots and additional basal spots. Fringe unspotted; legs dark brown with apical white tarsal bands. Palpi, apical white band, two tarsal bands; carries malaria. Europe, Mashonaland. (2) *P. costalis:* Wing costa, four large and two small spots. On the first long vein two broken spots giving a pattern found besides only in *P. marshalli.* This spot is variable. Femora and tibiæ mottled with yellow. Tarsal banding involves to some extent both sides of the joint. Palpi, three narrow bands. Africa. (*P. costalis v. melas,* pale costal spots are absent, but it has the characteristic markings on the first long vein.) Conveys malaria, but probably is not associated with as high an endemic index as *M. funesta.* (3) *P. cinereus:* Wing, three white spots on the black costa. Wing fringe brown, with yellowish patches. Palpi, four bands; legs very thin, jet black. Apex of femora and tibiæ pure white, apices of fore and hind metatarsi have minute apical bands. South and British Central Africa. (4) *P. pitchfordi:* Three main costal spots, two basal small interruptions; sixth vein two spots. Fringe spotted at junction of long veins. Legs black, with apical pale spots to segments. Thorax broad white band in middle. Zululand. (5) *P. marshali:* Distinguished from *P. costalis* by the palpi; two broad apical bands, one small basal one. Mashonaland. (6) *P. jeyporensis:* Costa black, two large white spots on the apical half and two or three small ones at the base. Fringe spotted. Palpi black, with three white bands, the broadest apical. Madras. (7) *P. chaudoyei:* Wing, six black costal spots, legs unbanded, a pale knee and tibial spot on the hind legs. Palpi, apex black and three narrow white bands. Algeria. (8) *P. palestinensis:* Wing costa, five large black and five yellowish spots of unequal length; legs brown; a pale spot at junction of tibiæ and metatarsi. Palpi, three pale bands, the apex white. Distinguished from *P. superpictus* by the unbanded legs, spotted wing fringe, and uniserrated large fore ungues in the ♂; resembles *M. hispaniola* and *M. turkhudi*, but these have hair-like scales on the thorax, whereas *P. palestinensis* has rather broad flat scales; differs also from *P. chaudoyei* in the form of the large costal spot, in the apical half of the sixth long vein being dark, and in the presence of a deep brown median thoracic line. Palestine, Cyprus. (9) *P. minimus:* Wings, three nearly equal spots and an apical spot. Fringe spotted, except at sixth vein; so distinguished from *P. superpictus*. Legs, no trace of banding or knee spots. Mid ungues straight; fore ungues curved. Hongkong. (10) *P. atratipes:* Clypeus trilobed, costa uniformly black, six prominent patches of scales on the veins. Australia. (11) *P. merus:* Resembles *P. cinereus*, but distinguished by the spotted and banded femora and tibiæ, also by its broader fringe spots. Has a single spot at the base of the fifth long vein. Africa.

Genus 6: *Arribalzagia:* (1) *Ar. maculipes:* Hind and midlegs much speckled and banded. Almost certainly transmits malaria (Lütz).

Genus 7: *Myzorhynchus:* (A) Palpi unbanded—(*a*) Last hind tarsus brown. (1) *Mr. barbirostris:* One fringe spot. India, Malay. (2) *Mr. pseudobarbirostris:* Resembles former, but distinguished by its speckled femora and tibiæ. Philippine Isles. (3) *Mr. bancrofti:* Several fringe spots. Australia. (4) *Mr. umbrosus:* No fringe spot, only one costal spot, Malay. (*b*) Last hind tarsus white. (5) *Mr. albotæniatus:* Other hind tarsi much banded. Malay. (*c*) Last two hind tarsi white. (6) *Mr. coustani:* Madagascar. (B) Palpi banded, last hind tarsus brown. (7) *Mr. sinensis:* One large yellow costal spot; wing fringe, one pale spot. China. (8) *Mr. vanus:* Wing fringe unspotted; apex of palpi white; costa two yellow spots; wings distinctly spotted. India, Malay, Philippines, etc. (9) *Mr.*

pseudopictus: Wings without prominent spots. Europe. (10) *Mr. minutus:* Wings, two white costal spots. Panjab. (11) *Mr. nigerrimus:* Apex of palpi, black.* India. (C) Palpi banded, last hind tarsi white. (12) *Mr. mauritianus:* Two hind tarsi white; wing fringe entirely brown. (13) *Mr. ziemani:* Two and two-thirds hind tarsi white; small pale spots at middle of costa, and an apical wing fringe spot. Africa. (14) *Mr. paludis:* Three hind tarsi white. Africa.

Genus 8: *Nyssorhynchus:* (A) Legs unspeckled: (1) *N. fuliginosus* (= *A. leucopus* Dönitz): Costa four large and one or more small spots. Mid-femora, pale spot near the apex. Hind tarsi three and one-fifth pure white. Palpi, apex white, then two narrow bands. (2) *N. karwari:* One and one-fourth hind tarsal segments white. Conveys malaria (Adie). (B) Legs speckled: (3) *N. stephensi* (syn. = *A. metaboles* Theobald): No segment of tarsus pure white; legs brown, speckled with white. First long vein has two typical spots beneath the third main spot on the costa. Fringe dark, with pale areas. Palpi two broad apical white bands, one narrow basal. White scales between the last two bands. India. (4) *N. maculatus:* Resembles *N. stephensi*, but easily distinguished by tarsi. Last segment of hind tarsi pure white. Hind tarsi broad white bands. Femora, tibiæ, and tarsi speckled with creamy bands. Fore and midtarsi, narrow yellow bands. Palpi, four bands, two unequal apical, then a small one, and a fourth nearer the base. India. (5) *N. theobaldi:* Wing, costa with five spots and an apical spot. Legs brindled with white scales and a large subapical white patch on the femora. Two and one-quarter hind tarsi pure white, then a black band, then a small white one. Palpi, two apical equal white bands, a third narrow one. *N. theobaldi v. nagpurensis:* Two and one-half hind tarsi white, tips of palpi black. India. (6) *N. maculipalpis:* Legs speckled; three and one-fifth hind tarsi pure white. Palpi, two white apical equal bands and a third narrow one. Palpi speckled with white. India, Africa. *N. maculipalpis v. indiensis:* Hind legs not so banded as in the type. (7) *N. jamesii:* Fore femora and tibiæ more or less speckled. Femora and tibiæ of hind legs with an apical white spot. Three and one-fifth hind tarsi white. Palpi white, apical broad band, and two narrow bands; resembles *N. fuliginosus*, but easily distinguished by speckled legs. A much smaller and paler mosquito than *N. maculipalpis.* (8)

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* White, according to Jones and Liston, who, moreover, do not distinguish between *vanus*, *sinensis*, *minutus*, and *nigerrimus.*

N. prætoriensis: Resembles *N. maculipalpis,* but palpi not mottled, and the two apical bands are further apart. Third hind tarsus has a small black patch near its base. First tarsus (metatarsus) mottled and has a broad white apical band like the second tarsus. Two hind tarsi white. Africa. (9) *N. deceptor:* Terminal half of proboscis white, terminal half of palpi white, with only two black rings, whereas *M. punctulatus* has three; distinguished from *M. leucosphyrus* by having only a small light spot at tibiometatarsal joint and not a broad band. Sumatra. (10) *N. willmori:* Differs from *N. maculatus* in having many scales on the abdomen (James and Liston). India. (11) *N. annulipes:* Femora and tibiæ banded. Tarsi, basal and apical bands. Palpi, apices of last three segments have white bands; first and second segments have white scales above. Australia. (12) *N. masteri:* Resembles former, but proboscis pale at the apex in the ♀. It is also a smaller species than the former. Australia. (13) *N. philippinensis:* Pale spot at apex of tibiæ. Three and one-fifth hind tarsi white. Palpi golden brown, broad apical band, then two narrow basal ones; resembles *N. jamesii.* Philippine Isles. (14) *N. nivipes:* Costa white, with four black spots; resembles *N. stephensi* closely in the wing spots, but the thoracic scales are spindle shaped, not narrow curved, and the legs are not speckled; resembles *N. maculatus,* but differs in having—(1) Midungues of male not simple; (2) has three and one-fifth hind tarsi white.

Genus 9: *Cellia:* (A) Last hind tarsi white: (1) *C. pulcherrima:* Three and three-quarters hind tarsi white. Panjab. (2) *C. bigoti:* Three hind tarsi white. Chile. (3) *C. pharoensis:* One and one-third hind tarsi white. (*C. albofimbriatus,* a variety of this.) Wing fringe uniformly pale. Egypt, Gambia. (4) *C. argyrotarsus:* Half the hind tarsus white; deep black basal band to last tarsus. Palpi, three bands. West Indies. (5) *C. albipes:* Half the hind tarsus white. Palpi two bands, conveys malaria (according to Pajos). West Indies and Brazil. (B) Last hind tarsi yellow. (6) *C. kochi:* Three hind tarsi yellow; thorax with "eye" markings. Malay. (C) Last hind tarsus black. (7) *C. squamosa:* Africa.

Genus 10: *Aldrichia: Al. error:* Slightly resembles *M. rossii;* easily told by the flat abdominal scales.

Genus 11: *Lophoscelomyia: L. asiatica:* A very small anopheline. Wings five black spots and four yellow costal spots. Malay.

Genus 12: *Christya: Ch. implexa:* Fore femora with white spots and a prominent pale band. Hind tarsi black; apex of leg white. Uganda.

We thus have a total of nearly 100 *Anophelinæ*. Even at the present day so little advance has been made in the study of the exact distribution of the different genera that it is impossible to say what light, if any, knowledge on this point would throw. Many observers are still content with saying that "the anopheles was found," without proceeding to inquire what genus or species, much less to inquire if the anopheline found was infected or not. To this point we shall return in considering the relation of the *Anophelinæ* to malarial endemicity. We may now consider some general points in the natural history of the *Anophelinæ:* the ova and the larvæ, and finally the adults in relation to endemic malaria.

THE OVA OF THE ANOPHELINAE.

The eggs are generally laid upon a floating object, though also upon the surface of water or *moist* mud. They are laid in a piled-up mass, even when deposited on the water, but these masses are quickly dispersed by currents in the water or by the wind, and the eggs then form the well-known patterns in triangles or parallel lines. About 100 eggs are laid, and the size of the egg varies from ½ to 1 mm. The eggs are boat-shaped, flat on the upper surface, and convex on the lower surface. The broad end of the egg contains the head of the larvæ, and is the dependent end when the egg is drawn up by capillarity on the sides of a vessel. The upper surface is granular or reticulated in appearance. This surface is continuous with the extremities of the ovum, and at the point of junction several polygonal areas can be seen. The lower surface is smooth and dark gray, but in some species is marked out in hexagonal areas. From this, however, may be detached a silvery membrane representing the follicular epithelium of the ovum. The delicate chitinous covering of the whole ovum is modified laterally into two prominent structures known as "*the floats.*" They consist of folds or transverse corrugations of the chitinous envelop in which air is contained. By means of this arrangement the eggs float on the surface of the water. Their general shape is oval, but they vary in shape and extent in the different genera. Along the margin of the upper surface the chitin shows a frill-like arrangement which is usually transversely striated. The width of this frill and its relation to the floats vary much in different ova. The ova of the *Anophelinæ* have so far been very little examined, but in the Indian *Anophelinæ* hitherto described there are three distinct types of eggs: *Type* 1: Ova have the upper surface very narrow, with the lateral floats not touching the upper margin. Ova of this type are found in *Mr. barbirostris, M. listoni,* etc. *Type* 2: Ova having a more or less broad upper surface, with the lateral floats touching the margin. Ova of this type are found in *M. rossii, Ce. pulcherrima,* etc. *Type* 3: Ova with no floats and with upper surface rudimentary. Only one anopheline is known with ova of this type, viz., *M. turkhudi.* It is interesting to note that ova of type 1 are found in natural waters or streams, whereas

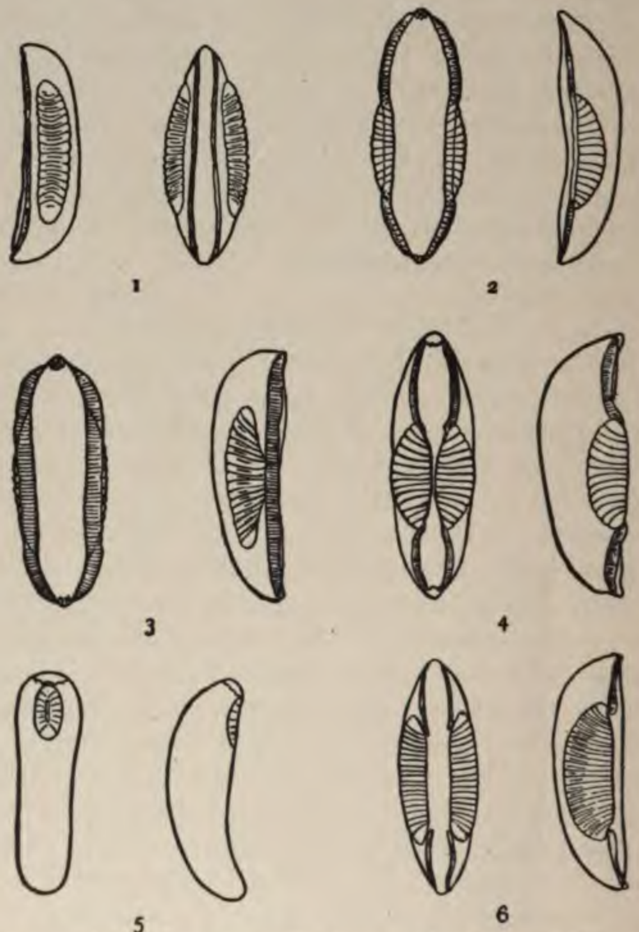

FIG. 7.—EGGS OF ANOPHELINÆ (from Stephens and Christophers' "Practical Study of Malaria").

1, *M. culicifacies;* 2, *C. pulcherrima;* 3, *M. rossii;* 4, *N. stephensi;* 5, *M. turkhudi;* 6, *N. maculipalpis.*

those of type 2 are found in pools. Further, there is an interesting difference between the arrangement or patterns taken up by the eggs of different species. Thus, Grassi had observed that the eggs of *A. bifurcatus* arranged themselves in star patterns, while those of *A. maculipennis* were arranged side by side, like a bridge of boats. This difference is dependent on whether the eggs belong to type 1 or type 2. Now the egg of *A. maculipennis* has been carefully described, and it belongs to type 2—*i. e.*, with the upper surface more or less broad and the floats touching the lateral margin; so that this egg conforms to the rule which was found to hold good for a variety of eggs examined by Christophers in India. It must be left for future work to explain what the exact reason for this difference depends upon; at present we only know that the ova with the floats not reaching the lateral margin are found in open natural waters or streams. Further, within each type there exists considerable variation. Thus we may find that—(1) *The frill* varies in width, in extent (in its middle third it may be replaced by the floats), in the amount of striation, or it may be represented by a striated margin only. (2) *The floats* may be oval, globular, etc. (3) The eggs may or may not be ornamented on the lower surface with a reticulated pattern. With regard to the single representative of type 3, viz., *M. turkhudi*, it is evidently a most aberrant form. It approaches, indeed, both in its larval and in its egg characters, to the characters of the larva and egg of a culex. Thus the upper surface of the ordinary egg of the *Anophelinæ* is represented only at the broad end of the egg by a small oval area. This is glistening and striated, and probably corresponds to the upper surface of other eggs. The egg is quite devoid of any floats. At the thick end there is a pale area with indented edges. The eggs of *M. turkhudi* are, however, laid in a heaped-up mass on a floating body, like those of other *Anophelinæ*, but it is a remarkable fact that when placed on the surface of water they sink to the bottom.

Duration of the Egg Stage.—Most of the observations on this point have been made in temperate climes. Thus Nuttall and Shipley give as the times for *A. maculipennis*, two to three days, while Howard gives for the same species three to four days, the longer time being in the colder month of April, the shorter in May. With regard to the power of resisting desiccation, experiments made by myself and Christophers in Sierra Leone showed that eggs dried on blotting-paper would hatch after an interval of twenty-four to forty-eight hours, on being placed on the surface of water, while after forty-eight hours none hatched out. If, however, eggs are preserved on damp mud and kept for forty-eight hours and then transferred to water, larvæ hatch out in a minute or two and the process may readily be observed under the microscope. But an exposure to the sun of twelve hours (in India) of eggs deposited originally on soft mud is sufficient to kill them so that none hatch on the addition of water. On *moist* mud eggs may still be alive after several days.

LARVAE.

Hatching of Larvæ.—A cap-like piece of the thick end of the egg-shell is split off. This cap is not defined on the egg, but the separated portions are of about the same size.

The larva consists of head, thorax, and abdomen, and on each of these parts structures occur which are in themselves of great interest and are of great importance in the identifying of larvæ. The head is globular; in the newly hatched larva it is very dark, and it is only later that it becomes lighter and that the chitinous patterns, often characteristic in arrangement, appear; and its size proportionately to the thorax diminishes, so that eventually the thorax is larger than the head. Further, in the young larvæ the important structures known as palmate hairs are imperfectly developed, but larvæ newly hatched can at once be told from those of *Culicidæ* by their characteristic horizontal position. The head is inclosed in a chitinous covering which, posteriorly, where the neck is inserted, is defined as a broad blackish collar. There is a slight fissure in this band dorsally, and it is from here that a V-shaped line diverges. This V often has grouped about it patches of pigment arranged in so characteristic a way that one is enabled to identify the species sometimes by this means alone. Thus *A. maculipennis* has a T-shaped pattern, while *A. punctipennis* has three transverse bands. Arising from two lateral protrusions on the anterior portion of the head are the antennæ. They consist of a single rod-shaped, somewhat curved body, bearing at the extremity two leaflets or bristles between which arises a branched hair. The antennæ is covered with small spines, particularly along the inner border, where they are arranged in pairs. At the junction of the proximal and middle third is a papilla bearing a hair. This hair is of importance in the identification of larvæ. Here again very few of the *Anophelinæ* have been so far examined, and the only data are those of Christophers and myself regarding the Indian *Anophelinæ*. We find that—(1) In the majority of the *Anophelinæ* it is simple and unbranched or even absent, while (2) in *A. lindesayi* it is short and tufted, and in *Mr. barbirostris* it is long and distally branched. These differences enable one to separate out these larvæ by inspection with a low power of the microscope, which is often a matter of great convenience. Of more importance than these hairs are certain hairs which occupy the most anterior portion of the head and may be called frontal or clypeal hairs. These hairs must not be confused with others which lie behind them. Thus slightly behind the level of the antennæ may be found a row of six-branched hairs, and behind these again a row of smaller branched hairs, which are, to a certain extent, variable in different species. It is, however, the variation in the clypeal hairs that affords a ready and important means of distinguishing species. *Anophelinæ,* which in the adult stage may closely resemble one another, may be quite different in their larval characteristics, and if we are right in assuming that difference in oval and larval structure constitutes a specific difference even if the adults closely resemble one another, then in these hairs we often have a ready means of distinction. Where there is no question as to the identity of the imagos, we have in these larval characters a mode of easy identification, though it does not follow that different species can all be distinguished by these larval characters. These hairs project from the anterior margin of the head and directly overlie structures which we shall mention later, known as the "shaving-brushes." The clypeal hairs are generally four in number, two arising from the extreme point near the middle line and two from the lateral angles of the clypeus. There may also occur two small hairs, making a total of six, immediately behind the anterior set. The following variations may be found: 1. The clypeal hairs may be quite simple—*i. e.*, unbranched; *e. g.*, *M. rossii, N. stephensi, M. culicifacies, M. listoni, M. turkhudi, A. bifurcatus.* [In *A. bifurcatus* variations in these hairs have been described by Ed. Sergent. Thus among 46 larvæ examined, three types were found: (1) Eighteen with both hairs simple; (2) 25 with the inner hair simple and the outer hair with two or three terminal branches; (3) three with both hairs slightly branched along their whole extent.] 2. The clypeal hairs may show slight branching, varying in degree in different species; thus in *N. maculipalpis* and *P. superpictus* it is but little developed, while in *P. jeyporensis* it is more regular and better developed. 3. The outer pair may be markedly branched, the median pair having a few inconspicuous branches; *e. g.*, *Ce. pulcherrima* and *Myz. pseudopictus.* 4. The other pair may be developed into a close tuft or cockade; *e. g.*, *Myz. sinensis*, *Myz. barbirostris*, *A. punctipennis*, *A. maculipennis*. (In the last the central hairs are figured by Grassi as not actually branched, but as splitting up at their ends into several filaments, while Nuttall and Shipley figure them as distinctly branched. The larva of *M. turkhudi*, aberrant in so many other ways, is peculiar in that the small hairs behind the clypeal set, instead of being short and inconspicuous, are long and easily seen. It may be well to state here that the hairs should be examined when the shaving-brushes are in a retracted position.)

We may briefly consider the mouth parts of the larvæ, though they do not suffice for distinguishing species. Situated laterally just beneath the lateral pair of clypeal hairs are two conspicuous whorls or tufts of dense hair, resembling a shaving-brush in appearance. These are the feeding brushes; they can be turned downward and inward to the center, and assist in producing the flow of food-particles into the mouth. While feeding, they are flexed and extended with great rapidity, and on the cessation of feeding they are rapidly extended, as if with a quick jerk. Below the feeding brushes we find on either side the mandibles, then the maxillary palpi, and most ventrally the maxillæ. These come inward and almost meet in the middle line, forming the floor of the mouth. Between them and slightly posterior in position lies "the under lip" of Meinert, conic in shape, and bearing teeth, which, as we have seen, are of generic importance in some of the *Culicidæ*, but with regard to the *Anophelinæ* no data exist. The mandibles bear stiff hairs directed inward to the mouth, and they serve to "comb" the feeding brushes. Further, on the maxillæ there are a set of fine teeth which are probably used for the same purpose. It should be added that the larva generally rotates its head through an angle of 180° when feeding, as may be observed by watching the process under a low power of the microscope, placing the larva for that purpose under a cover-glass or in a watch-glass.

Food of Larvæ.—This is mostly supposed to consist of unicellular organisms, fresh water algæ, diatoms, but the larvæ of *Anophelinæ* may also exhibit cannibalism. The exact nature of the food of larvæ has been little studied. Most of the data on the subject refer to the vegetable organisms that are found in the water from which the larvæ were collected. It is generally stated that they feed on fresh-water algæ,—*Spirogyra*, *Mougestia*, *Protococcus*, etc.,—but in the stomach may also be found *Protozoa*, and it is possible that these form a considerable portion of their food; on the other hand, vegetable matter is certainly consumed, and may be found in the intestinal contents, and the green color of larvæ is in part but not entirely due to this cause. A peculiar fact which one often observes in larvæ derived from foul puddles is that the body is almost entirely covered with a mass of *Vorticellæ* or allied organisms. Again, to determine the vegetable organisms present in every water frequented by larvæ would be a large task, and it is doubtful how far one would derive any especial advantage therefrom. We may, however, name the following plants, found in waters infested with *A. maculipennis*, and which were collected by Ed. and Et. Sergent in Algeria. They were *Myriophyllum, Elodea canadensis, Elatine alsinastrum, Ranunculus* (*Batrachium*), *Nymphæa alba, Nuphar luteum, Trapa natans, Limnanthemum nymphæoides, Hydrocharis morsus-ranæ, Alisma natans, Potamogeton spp., Lemna spp.* With regard to *Lemna*, we have repeatedly observed that "tanks" in India and pools covered with it do not harbor larvæ, though in favorable situations; whether or not the exploration is, as has been suggested, that it offers a mechanical obstruction to the movements and existence of the larvæ remains to be shown; on the other hand, a small amount of *Lemna*, according to Grassi, favors the growth of larvæ. In the intestinal contents we find also bacilli, and among these the "molds," identical with those which, as we have previously seen, Schaudinn finds in the esophageal diverticula of the adult.

The Thorax of the Larva.—In the young larva the thorax is not so broad as the head, but in the adult nearly twice as large. The thorax is furnished with numerous hairs or bristles, which are not of importance for purposes of recognition of species, but in some species we find on the thorax hairs identical with those on the abdomen known as palmate hairs. They are situated posteriorly and laterally, and often require careful examination for their detection. They are well developed in *M. culicifacies, M. listoni*, and *P. jeyporensis;* they are not present in the majority of *Anophelinæ*, and are absent, for instance, in *A. maculipennis.* Those larvæ in which palmate hairs occur on the thorax are found in streams of water where there is considerable movement. *The abdomen* of the larva consists of nine segments, the first seven of which are similar in shape, decreasing in size as they reach the posterior end. The eighth segment is peculiarly modified, bearing the respiratory stigmata, and the ninth segment, on which the anus opens, is cylindric and bears various appendages. The first two segments in *A. maculipennis* bear at their posterolateral margins a pair of long branched hairs. The third segment carries a single similar pair. The other segments bear smaller unbranched hairs, and, further, there are shorter tufts of hairs on either side of the longer hairs, but these hairs do not appear to vary much in different species. On some of the segments, however, we find hairs of quite a different character. From their resemblance to a fan or the leaf of a Palmyra palm they are termed "palmate hairs." They lie nearer the middle line than the lateral hairs, and about half way between the front and back margin of each segment, though their position shifts toward the posterior margin as the hindermost segments are reached. They really consist of a number of leaflets or rays set upon a central little knob or stalk; when opened out, the leaflets are extended like the rays of a fan, and practically form a complete semicircle, or even a circle. They are seen in their extended position when the larva is suspended under the surface film of water, and, in fact, their function is to support the larva in this position. At other times, when the larva is beneath the surface, the fan may be seen closed and the leaflets huddled together. In the freshly hatched larva the fan is ill developed, but about the third day it has developed half a dozen lanceolate leaflets, which later take on the peculiarities of the particular genus and species to which they belong. The fully developed hair consists of about 15 to 20 leaflets, and from the position and characters of these hairs we can derive great assistance in the identification of species. We stated that the hairs are found only on certain of the first seven segments, and occasionally on the thorax. Thus we have: (1) Well-developed hairs on all segments, one to seven, including the thorax in *P. jeyporensis, M. listoni, M. culicifacies.* (2) Well-developed hairs on the second (or third) to seventh segments. (3) Rudimentary hairs on the first segment and even on the second, and on the thorax in *N. stephensi, N. maculatus, N. theobaldi.* (4) On the third, fourth, fifth, sixth, and seventh segments only *M. sinensis, M. barbirostris, A. maculipennis.* (5) On the fourth, fifth, and sixth segments only *M. turkhudi.* The commonest arrangement is the second one, viz., with palmate hairs on the second to seventh segments. But beyond the distribution of the hairs, which may not furnish much help, we have in the characters of the individual leaflets characters of specific importance. We can divide the leaflets into two portions—the basal portion, like an elongated wedge, and the terminal portion or filament, which joins the base of the wedge by a series of notches; or, without these, the basal portion gradually tapers into the filament. In some leaflets there is no sharp distinction between basal portion and filament; in others the filament is long and slender, and yet in others short and stumpy. We may find, then, the following types of leaflets: (1) The leaflets are unbrokenly lanceolate in shape, notched along the terminal half, and without a terminal filament—*e. g., Mr. barbirostris, Mr. sinensis;* (2) filament distinct and long—*M. rossii, M. culicifacies, M. listoni, N. fuliginosus.* Further, in this type we can distinguish one species from another; thus in *M. rossii* the filament is as long as the leaflet and the notch at the point of junction is wanting, while in *M. listoni* it exists. (3) The filament is very short—a spike-like process—*e. g., N. maculatus, N. theobaldi, N. maculipalpis.* In *M. turkhudi* the filament is short and blunt. With regard to the great majority of larvæ no observations on these points have yet been made.

The Respiratory Stigmata.—On the eighth segment are situated the openings of the tracheal system. There is in the *Anophelinæ* no projecting tube, as in other *Culicidæ,* but the openings are situated on the surface of a specialized area. This area is approximately quadrilateral in shape, and is bounded laterally by chitinous plates armed with teeth. No differences in the disposition, number, etc., of these teeth have so far been described in different species. The stigmata lie in the anterolateral corners of this quadrilateral area, and are protected by a hinged flap which bounds this area anteriorly. This flap, when the larva is breathing, is folded forward so that its dorsal surface looks anteriorly, and the stigmata are uncovered and are directly in communication with the air. When the larva proceeds to sink, the flap is folded back and the continuity with the atmosphere is broken. The variations in this most interesting structure have been so far not at all studied, and no doubt many differences exist in different species.

Lastly, on the ninth abdominal segment we have the opening of the anus. This segment is cylindric in shape and terminates posteriorly in a somewhat flattened surface, on the center of which opens the anus. Arising above the anus are four long branched hairs; they project posteriorly and overhang the anus. Arising below the anus, on a curved chitinous base on either side, is a large fan of branched hairs which, in the normal position, hangs ventrally downward and resembles a rudder. Further, arising from around the anus itself we have the four transparent, finger-like processes called the anal papillæ, in which tracheal tubes are seen ramifying; two of these are ventral, two dorsal, symmetrically placed. In these structures and in the various hairs of these regions there does not appear to be much variation in different species.

Habits, Breeding-grounds of Larvæ, etc.—The movements of the larvæ of the *Anophelinæ* are, as we have already said, characteristic when disturbed; they may "skate" along the surface horizontally, progressing with backward jerks, or, if they seek the bottom, they rapidly dart below with forcible wriggles. They lie at the bottom quite motionless, and may be poked about before they will give any signs of life. Undoubtedly this lifeless position is assumed by them for protective purposes. In a few minutes they usually rise, but their immersion may be prolonged to one-quarter of an hour. The motion to the surface is effected by a series of backward jerks until the surface film is penetrated, when often at once the head rotates, the mouth faces dorsally, and the brushes begin their vigorous sweeping movements.

The Duration of the Larval Stage.—Here again no absolute value can be given, the duration being determined by at least two main factors: (1) Food; (2) temperature. That food is a very important factor is shown by laboratory experiments, where if the larvæ are kept in a glass dish filled with tap-water only, little or no growth is effected; while again temperature is of great importance, as shown by the "hibernation" of larvæ through the winter in temperate climes or through the "cold" weather of the tropics. The larval stage of *A. maculipennis* was found by Nuttall and Shipley to last eighteen to twenty-one days, at a temperature, at first, of 16° to 19° C., and later of 23° to 26° C. Similarly Howard gives the larval stage of *A. maculipennis* in America as sixteen days, while Grassi, for the same species in Italy during the summer, gives the duration as twenty to twenty-two days. Similarly for *Ce. argyrotarsis* Lutz gives the time of *total* development as three weeks at a temperature of 25° C. That the duration of the larval stage in the tropics is less than in temperate climes is shown by the examples, already quoted, of two anophelines, viz., *Cellia argyrotarsis*, twelve days; *M. rossii* (temperature of water, 96° to 102° F.), eleven days.

Desiccation of Larvæ.—Celli and Casagrandi have made experiments on this point and find that anophelines can resist desiccation at 20° C. for two days; at 35° C. for one day; and at 40° C. for two minutes only, while also the pupæ cannot survive longer this degree of temperature. It is interesting also to note that larvæ were found to exist on moist earth for four days. Christophers finds that larvæ stranded on mud which had dried so far as to lose its glistening surface did not come to life on the addition of fresh water.

Moulting of Larvæ.—During this time the larva undergoes one or more moults. Not infrequently during this process the position of the larva is not quite horizontal, but is slightly inclined toward the surface, but at an angle not so great as that of *Culex*. The larval stage of the *Anophelinæ* may, however, be prolonged much beyond these limits. Thus in the case of *A. bifurcatus* some larvæ caught by Nuttall and Shipley on September 14, 1900, were kept through the winter; only one survived, and that pupated on March 19, 1901 (the imago taking eleven days longer to hatch), the larval stage thus lasting seven months; and there are a number of observations which show that this is one method, viz., the hibernation of larvæ, by which mosquitos survive during the winter.

Hibernation of Larvæ.—James, in Lahore, India, found that in permanent breeding-places larvæ of *M. culicifacies* could be found in a hibernating condition throughout the winter (temperature, 55° F. about); their movements were sluggish and they grew extremely slowly, if at all. None were seen to develop into pupæ, but it is not safe to conclude that this applies to all species, for it was not so at Lahore, where in the case of *Ce. pulcherrima* and *N. fuliginosus*, eggs, young larvæ, and pupæ were found in new breeding-places formed during the winter. That larvæ are capable of withstanding low temperatures is shown by Galli-Valerio's and Narbel's observations. They found the larvæ of *A. bifurcatus*, but not of *A. maculipennis*, below the ice in Switzerland. Others have actually found larvæ of *Culex pungens* frozen within the ice. When thawed out, the larvæ were alive and eventually developed into imagos. But it must not be inferred from these observations that this is the sole method by which mosquitos tide over the winter. For instance, Grassi observed that *A. bifurcatus* hibernated chiefly in the larval form, finding the larvæ in midwinter in Italy, but the imagos rarely, but that this was not the case with *A. maculipennis:* no larvæ of this species could be found (in Holland they first appear about the middle of May), while the imagos were plentiful in outhouses, huts, etc. So, also, Nuttall and Shipley found that of a collection of larvæ of *A. bifurcatus* and *A. maculipennis* kept in the laboratory the larvæ of the latter all died during the winter, whereas the former lived. So, also, Theobald observed a number of larvæ of *A. bifurcatus* during November in England, and found that by the end of December only 2 per cent. had pupated. It is not likely that any seasonal cessation from pupation occurs in the tropics, except where there is a definite "cold weather." We shall see later that the imagos can exist for some time during the "dry season," when no opportunity for breeding occurs.

Habitat of Larvæ.—It is perhaps not too sweeping a statement to assert that mosquitos (*Anophelinæ*) will breed in any collection of water if they are unable to find their natural breeding-places elsewhere. That which in the early days of the mosquito-malarial discovery was described as the "anopheles pool" no doubt exists, but it would be perhaps truer to state that the majority of the *Anophelinæ* are found in collections of water of all descriptions,—streams, canals, swamps, marshes, etc.,—which can hardly be designated by that name. Over and over again will the unwary observer be deceived if, after making a superficial inspection, he concludes that there is no possible breeding-ground present. Man cannot exist without water, and where there is water, whatever its source, it would be rash to deny the existence of larvæ until every nook and cranny had been thoroughly explored. The water may exist in a hidden cistern on the roof of the house, or may occur at the bottom of a forty-foot well; yet in both these structures the larvæ of *Anophelinæ* may be found. In the smallest collections of waters; in the tins filled with water that protect the legs of tables from the attacks of white ants in the tropics; in broken bottles used to adorn a chieftain's walls; in the collections of water in the leaves of tropical plants, such as the pitchers of pitcher plants; in the mouths of old disused cannon; in barrels; kerosene tins; in the smallest "pockets" of water collected in solid rock; in the bottom of old boats; in the foot-prints of cattle; in the jars used for storing water against fire; in pig troughs; in fact, in every possible collection of water the larvæ of the *Anophelinæ* may be found. Again in shallow puddles, "tanks," reservoirs, aboard ship in the bilge water, in lakes, disused quarries, streams, canals, swamps, marshes, deep wells, rivers, in brackish water and even in the sea—in all these places larvæ may occur. We must, however, consider the question of the sources of larvæ more closely, and point out with what reservations some of the above statements must be made. And, firstly, it must be recognized that a simple naked-eye inspection of a source of water is insufficient if there is any floating matter to obscure the view, and even if there is not, minute larvæ may escape notice. In all cases the larvæ should be "fished" for by dipping into the water with some convenient utensil, such as a white enameled cup or ordinary tin mug. Now it is to a great extent true that the breeding-places of the *Anophelinæ* and the other *Culicidæ* are different. In a native village in the gold coast examined by Christophers and myself the natives used tubs for storing their drinking-water. These tubs contained literally millions of *Stegomyia* larvæ, but never *Anophelinæ* larvæ. The latter bred in deep wells and in various small pools and larger collections of water a few feet deep, which existed even at the end of the dry season. These pools contained no visible weed, and were constantly exposed to the glare of the tropical sun. Similarly in Sierra Leone the source of *Stegomyia* larvæ was in the collections of water about houses, in domestic utensils, barrels, tins, etc., but it was exceedingly rare to find the *Anophelinæ* breed in these, for, as we shall see later, many species exercise great selective power in their choice of a breeding-ground, and the *Anophelinæ* larvæ in Freetown bred in the streams and in their back eddies, in the numerous rock pools existing during the rainy season, and in the collections of waters in badly made drains, etc. So that, broadly speaking, it is true that the *Anophelinæ* select other breeding-grounds than the other *Culicidæ*, and this may depend upon whether the water provides suitable food for one or the other. On the other hand, this does not preclude their being found together, but it would appear to be commoner for the larvæ of the other *Culicidæ* to be found in what may be regarded as a typical breeding-place for the *Anophelinæ* than to find the reverse; thus it is commoner to find, say, *Culex* and *Anopheles* together in a shallow pool than it would be in a tub. It is noteworthy also that when occurring together the proportion is not an even one, but there is frequently a preponderance of one or the other. But perhaps no strict statement could be made on these points. It is, moreover, true, on the whole, that anophelines are not found breeding in the foul, dirty waters affected commonly by *Culex* and *Stegomyia*, such as cess-pits. The *Anophelinæ* prefer, no doubt, clearer water than the others, and there may be a further reason for their not occurring together more frequently and in a more even proportion, viz., that they would be devoured by the more developed cannibalism of their more powerful relatives. Although, then, the *Anophelinæ* and the other *Culicidæ* may be found breeding together, yet we require further observations before we can satisfactorily explain the matter. Again, in certain regions in the tropics, in native huts, the number of *Anophelinæ* may far outnumber the others, and this is probably the normal condition unless there is an unwonted supply of artificial breeding-grounds, as in the instance noted above. So in many native huts examined by us in Africa and India the *Anophelinæ* swarmed in the houses, dotting the thatch like so many minute stalactites, and *Culex*, etc., might be difficult to find, and likewise the breeding-grounds would yield almost entirely *Anophelinæ* larvæ. What determines the distribution of the culicides—in fact, why, for instance, in certain of the West Indian islands the *Anophelinæ* are absent though *Culex*, etc., abound—we cannot at present say. There are certain factors, however, which appear to determine the occurrence of larvæ in particular waters. Thus in temperate climes they are not found so frequently in shaded pools as in waters exposed to the sun, but here again there is no hard-and-fast rule, for the larvæ of the genus *Lophoscelomyia* are found in collections of water in split bamboos, where little or no sunlight reaches them. As expressed by Meinert, "elle n'aime pas l'ombre des grands bois mais récherche le soleil et la lumière." In the tropics one is at first surprised to find that many likely breeding-places yield no larvæ. Some of the reasons for this are the following: (1) The source of water is too large; thus the larger "tanks" in India are often quite free from larvæ, even where there are no fish. The probable reason is that they are too much exposed to the action of winds, though, on the contrary, one finds larvæ in smaller pools on which one may see waves constantly breaking on a windy day. It is possible that the depth of the water has some inhibiting effect, for, generally speaking, deep waters are not selected by mosquitos. (2) The explanation is often a simple one: the pools contain fish, many species of which are extremely destructive of larvæ. (3) The pool or reservoir contains a coating of species of *Lemna*. Many observers have noticed the fact that excessive growth of *Lemna* is inimical to larvæ. The explanation is generally assigned to a mechanical action on the larvæ preventing their rising to the surface, but it has not, however, been shown that the imagos have really deposited their eggs in such waters, and often the amount of *Lemna* present seems insufficient for it to have a mechanical action. With regard to the kind of water on which the *Anophelinæ* will lay eggs, Christophers and myself made some experiments in Calcutta. We could find, however, no selective action in the water chosen by *M. rossii* for depositing eggs. Pure water, green stagnant water, or foul sewage was indifferently selected. (4) Occasionally, also, larvæ have been absent in artificial cement tanks, though present everywhere else in the neighborhood. One was forced to attribute such absence to the effect of wind, in the absence of any more satisfactory explanation. (5) Larvæ, too, we found were generally absent in fresh spring water at its source, though this was not always so, for larvæ were found by Christophers and myself at elevations of 7000 feet and 4000 feet in spring water, removed from human habitations, though in these cases, from the nature of the mountains in the dry weather, there was no other possible breeding-places for miles around. Larvæ have been found by various observers in brackish water; thus in Lagos they occur in water containing 0.6 per cent. of salt, but they have been found in water containing as much as 4 per cent. of salt in Algeria (*A. maculipennis*), and by Bancroft in Australia in the sea (*N. annulipes*).

Enemies of Larvæ.—Fish, as we have already pointed out, and as has been confirmed by many observers, devour larvæ greedily, but, on the other hand, fish and larvæ may occur together. The reason for this may be twofold: (1) That the larvæ are protected by a sufficiency of weed; (2) that the particular species of fish is not one that specially feeds on larvæ; thus in experiments made on common fish of the Indian tanks some, such as catfish and carp, either devoured them very slowly or not at all, whereas six young barbels devoured about 100 larvæ in a quarter of an hour. Larvæ have a great many enemies to contend with, such as *Libellulidæ* larvæ, *Dytiscidæ*, those of *Agrionidæ*, *Chironomidæ*, *Nepidæ* (water-scorpions), *Notonectidæ* (water-boatmen), etc., and their larvæ. Some of these devour larvæ very rapidly; the process can readily be watched by placing the enemy and the larvæ together in a tumbler of water. There is still one important point with regard to the destruction of larvæ which remains to be illustrated. It was at first thought that the *Anophelinæ* and their larvæ were not found far from the haunts of men. This, however, is true only in a measure, for from the instances already quoted it has been shown that *Anophelinæ* exist on remote mountain-tops, far from human habitation, and they are not uncommonly found in jungles some miles, at least, distant from habitations. But, as we shall see immediately, it becomes important in all these questions to know exactly what species of the *Anophelinæ* we are dealing with, and many observations made not only take no regard of this point, but even do not distinguish between the *Anophelinæ* and the *Culicinæ*. Now, if we examine the larvæ in the neighborhood of a tropical village, we are astonished to find that in the pools about the native huts larvæ of one or more kinds abound, but if we then extend our search to other sources, *e. g.*, a neighboring stream, a lake, or a canal, we find that no longer are the larvæ those of what we may term foveal or "domestic" mosquitos, but they belong to a quite different number of species, the non-foveal or "wild" mosquitos. If we take a particular instance, the matter will become clearer. We will suppose that we are examining all the breeding-ground in the neighborhood of a native village in India. In the pools, puddles, and collections of dirty water about the huts we find the larvæ of *M. rossii* and no other larvæ. If we next examine collections of water containing much weed, in ditches, and small swamps, ponds, etc., we find that the larvæ of *M. rossii* are completely absent in these, and we find possibly the larvæ of *Mr. nigerrimus;* and the converse is true, that these larvæ are never present in dirty shallow puddles about the houses. This holds good not only for these larvæ, but for many others. Thus, while the breeding-grounds of *M. listoni* and *M. rossii* may be adjacent, yet

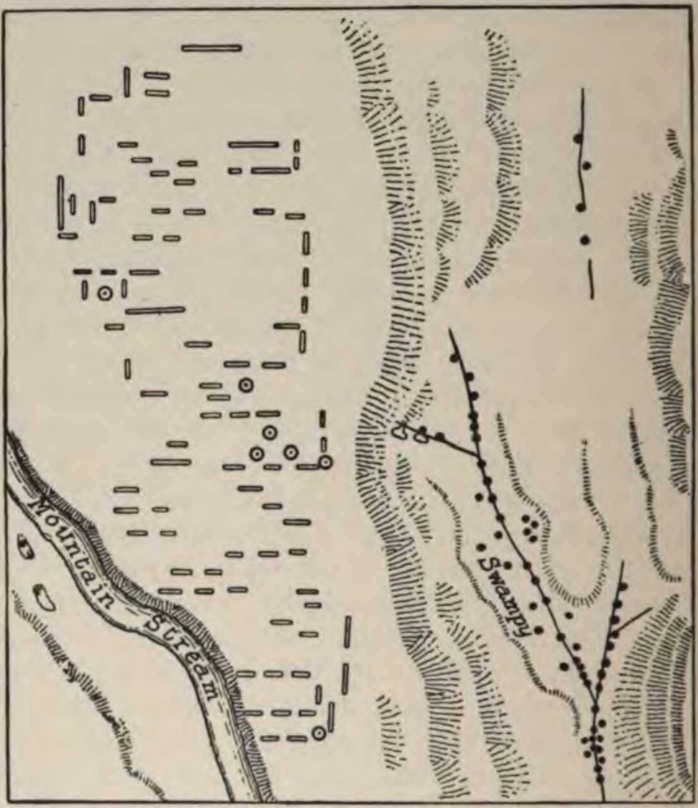

FIG. 8.—PORTION OF COOLIE LINES ON A TEA PLANTATION TO SHOW DIFFERENT BREEDING-GROUNDS OF *M. rossii*, *M. listoni*, AND *N. maculatus* (from Stephens and Christophers' "Practical Study of Malaria").
⊙ = *M. rossii;* • = *M. listoni* and *N. maculatus.*

they are not found together. *M. listoni* is found at the edges of streams and in swampy localities; *M. rossii*, in the dirty puddles in the immediate vicinity of the native huts. And, again, Christophers and myself found this peculiarity in India for a particular species, *N. stephensi*, that although there were numerous breeding-grounds at hand, yet this species was not found there, but, on the contrary, only in kerosene tins and earthenware pots. Again, to take yet another instance: on one side of a road was a weedy lake; on the other side, a small stream leaking out from the former; in the lake only *N. fuliginosus* was found, in numbers; in the small stream, only *M. culicifacies*. That mosquitos exercise a selection in the choice of a breeding-ground is very evident from these examples. Grassi, for instance, states that *A. maculipennis* is much commoner in dwellings than *A. bifurcatus*, which is a frequenter of woods, and than *P. superpictus*, which is found near swamps and marshes. This probably corresponds to differences in the habitat of the larvæ, but on the habitat of particular species very few observations have as yet been made. To this question of "domestic" and "wild" mosquitos we shall return in considering the habits of the imagos.

Larvicidal Bodies.—It will not be necessary here to consider in detail the various larvicidal bodies that have been used, for in practice, from reasons of cheapness and procurability, hardly more than one or two are used. Of these, petroleum, tar, or kerosene oil is the one that is most generally used, as it is cheap, always procurable, and effective. Among the many other bodies that have been used, one of the anilin colors, Larycith III,* has been found to exceed in potency all soluble larvicides. In dilutions of 0.00015 to 0.0003 pro mille it will destroy all young larvæ in a maximum time of seventy-two hours, or if dissolved in a mordant (1:1000 caustic soda), it will kill in thirty hours. At the same time, however, it destroys all aquatic life, being a soluble diffusible poison, but it is innocuous to mammals. The stronger solution is necessary to kill the larger larvæ, and the time required is somewhat longer, but of its efficiency there can be no doubt, and, moreover, it has the advantage that the solution remains active for about two months.

With regard to its cost: to destroy the larvæ in a cubic meter of water about 1.5 grams is the *maximum* amount required, the price being about a half-penny. With regard to kerosene oil, it is not so necessary to know the exact amount, for it is easily seen when sufficient has been added to form a continuous layer over the surface. However, Howard estimates that a quantity of oil costing about 18 shillings ($4.50) is sufficient to treat an area of 96,000 square feet. It is necessary, however, in the tropics to allow a considerable margin for evaporation, and larger quantities are required where the surface is covered with weed; in fact, in these cases difficulties occur in its application, and it is best to spray it on with a pump. Without entering here into a consideration of the practical application of this method, one may point out a difficulty experienced in applying it to the surface of flowing canal water. The kerosene oil in this case flowed down the middle of the stream and left the sides, where the larvæ sheltered untouched. It will often be found of advantage to mix the kerosene oil with soap solution or some oily material, such as the "ghee" of India; a more uniform layer is then obtained.

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* Larvicide, which is the commercial name of this dye, is supplied by Weiter-ter-Meer of Verdringen.

THE PUPA.

Celli gives thirty days as the time that elapses between the egg stage and that of the perfect insect (*Anophelinæ*) at a temperature of 20° to 25° C. These, after another twenty days, lay eggs, so that fifty days is the extent of a generation, or, at higher temperatures, as little as forty. Meinert considers that there are two or three generations of the *Anophelinæ* annually, according to the temperature. In the tropics, however, the duration of the larval and pupal stage is much less. Thus for *M. rossii* in India Christophers gives fourteen days as the minimum time, and about the same for *M. culicifacies* and for *Ce. argyrotarsis;* Taylor in Havana gives also fourteen days.

The pupa of the *Anophelinæ* is not so readily distinguished from that of other *Culicidæ* as is the larva by a naked-eye examination. The attitude, according to Howard, is more horizontal than that of other pupæ. A closer examination with a low power of the microscope reveals an easy mode of distinction in the respiratory trumpets. In the *Anophelinæ* they have a square, truncated end, and project from about the middle of the thorax. In *Culex* they are long and narrow and have a slit-like opening. In *Stegomyia* and other genera they are again different. Whether differences occur in the different genera of the *Anophelinæ* has not so far been established. The pupal or nymphal stage in the tropics lasts for about forty-eight hours. The change from the larval to the nymphal stage is a sudden one, but its details have not been minutely studied.

The change from the nymph to the imago we have already described. Various factors besides temperature influence the emergence of the imago. Thus, Howard found that creasote oil added to the water caused a violent struggling of the pupæ and the escape of the imagos, the pupal stage in this case lasting only fifteen hours. Pupæ taken out of the water and placed upon moist blotting-paper hatch out after a variable time, but if placed upon a dry surface, so that they become shriveled, flies rarely emerge. The pupal stage is the one that is most sensitive to excessive motion, so that the conveyance in tubes, etc., is difficult; but they may be subjected to the concussions of a railway journey of some hundred miles if they are given fresh air at each halt at a station.

We may now proceed to consider, as a group, the *Anophelinæ*, their distribution, habits, etc., and their relationship to malaria.

DISTRIBUTION OF ANOPHELINÆ.

It is possibly not justifiable to say that the distributions of malaria and of the *Anophelinæ* are identical, for there are many regions, or at least districts, of the earth where malaria is known to exist, and as yet observations are lacking as to the presence of the *Anophelinæ*, but it is absolutely true to say that there is no focus of malaria anywhere which, when examined for *Anophelinæ*, has failed to reveal them. It is hardly necessary to consider statements to the contrary: they result simply from ignorance. Such statements have been made only too often by those who do not know a sand-fly from a mosquito, much less a *Culex* from an *Anopheles*. They do not require serious refutation. If, however, we consider the distribution of the known *Anophelinæ*, we find that, although it is true that no malarial country or place exists without them, yet the converse is not true, and *Anophelinæ* can exist in a country without the occurrence of malaria. The well-known disappearance in England of malaria in the fen district and elsewhere has not been dependent on the disappearance of *Anophelinæ*, for these exist there now. And this is not an isolated instance, for elsewhere, as in parts of Italy, *Anophelinæ* exist where there is no malaria; similarly in the environs of Paris, in Holland, in northern Europe, *Anophelinæ* exist, where there is no malaria at the present day, nor, in many cases, has, as far as is known, ever existed. We shall see that this non-parallelism between *Anophelinæ* and malaria exists also in the tropics (India), but to this we shall return. We mention it here, as it makes us accept with great caution the common explanations given of the disappearance of malaria from certain areas, *e. g.*, the fen district of England. In this particular case the disappearance has been attributed to—(1) a diminution in the number of *Anophelinæ* consequent upon drainage. To this reason, in our opinion, little importance can be attached, for we know of no good reason to believe that the number of *Anophelinæ* has any great influence on malaria, provided, of course, that they do not become positively scanty, and this is not the case at the present day in these districts. (2) Emigration from the district. There is no evidence to show that this cause has been operative in districts in northern Europe where malaria has disappeared. (3) Quinin. This is a cause which, we know, could produce the effect, but we still have many cinchonized populations and yet malaria flourishes. It appears to us that none of these reasons is the real one, and that until explanations can be given of similar conditions found also in the tropics where none of these reasons apply, we must be content to assign these phenomena to unknown factors. We are not, then, in a position to explain the disappearance of malaria from a place where it formerly existed, nor can we say why malaria never has, so far as we know, existed and does not exist to-day in regions where there are *Anophelinæ*. It is hardly an explanation to say that malaria does not prevail there because there are no parasites there for the mosquitos to transmit. The difficulty is to explain why malaria has become established in one place and not in another in both of which *Anophelinæ* exist. Bearing in mind, then, the negative limitations of the main proposition, "No malaria without *Anophelinæ*," we may consider broadly—and even at the present day the facts at our disposal are far from enabling us to do so closely—some of the epidemiologic features of malaria. We can to-day explain most, if not all, the epidemiologic facts which common experience has accumulated during past centuries, and, indeed, where we cannot explain satisfactorily every statement that has been generally accepted, we are, since Laveran's discovery, in a position to put to the test the accuracy of the diagnosis of malaria by a microscopic examination of the blood. It is not until this has been done in these doubtful cases that we are certain of our facts, and whether we are not really attempting an explanation of what is not really a fact, but a misconception.

Relation to Temperature.—Malaria has a distribution roughly of 40° S. to 60° N. latitude, and is limited by the isothermal of 15° to 16° C. But there is a closer relationship than this to temperature, in the well-known seasonal outbreak of malaria which varies in temperate climes according to the temperature of the particular country. Thus in Germany and England the maximum temperature coincident with the outbreak of malaria occurred in August and September, while in Italy the malarial year, so to speak, begins in June. Wanzel, quoted by Ruge, who had made a close study of the epidemiology of malaria, had noticed that in Germany a mean temperature of 15° C. was necessary for the development of an epidemic, and that with higher temperature the malarial curve began to rise twenty days afterward, while at lower temperatures it rose twenty-five days later. Taking twelve to fourteen days as the incubation period for an attack, this gives six to eleven days as the time taken for the development of the virus. These facts showed that there was a close dependence on temperature, and further they correspond in a remarkable way with what we now know to be the effect of temperature on the time taken for the mosquito cycle, and also to the now established fact that a certain temperature is necessary before sporozoïtes develop at all.

Relation to Moisture.—Malaria has long been known as marsh fever, and its connection with low-lying water is universally admitted; but malaria also exists in apparently arid dry places. Even in pre-mosquito days this was explained by finding water in such places which had been overlooked, and instances of this still occur. The *Anophelinæ* require water to breed in, and, as we have said, no exception to the rule of their presence in malarial regions has yet been found. Now, temperature alone could not account for an outbreak of malaria, for in the tropics we have the converse condition, viz., a temperature uniformly high, and perhaps not varying more than a few degrees throughout the year, and yet a definite malarial season. Here again we find the explanation adequately supplied by the mosquito cycle. It is, at least in some parts of the tropics, not during the maximum of the rains that malaria most prevails, but a month or two later, in the season intermediate between the rains and the dry season. When the rains are decreasing in extent and violence, we find that there has been an immense increase everywhere in breeding-grounds, streams, ditches, swamps, pools, etc. This increase, indeed, occurs in the early part of the rains also, but it is perhaps at the end of the rains that it is greatest. The result is an increase in *Anophelinæ*, which, allowing a month for their full development, would occur later than the rain maximum. If, now, we consider that these *Anophelinæ* have to become infected (in seven to fourteen days), and further we have to allow time for the incubation period (seven to fourteen days) after they have bitten a fresh person, we see how it is that the maximum fever period should fall some time after the maximum of the rains. It would be well if this point were again accurately investigated by a determination of the "endemic index" month by month, for one objection that can be raised to the above data is the doubtfulness of the figures for the malaria morbidity month by month, as in popular opinion, at any rate, the most deadly malarial season in the tropics is most diversely stated, and by some as occurring even at the height of the dry season. *Anophelinæ* containing sporozoïtes were at all periods of the year found by us in the native huts. Gosio gives the following data with regard to monthly infection of *A. maculipennis* in Tuscany:

MONTH.	NUMBER EXAMINED.	NUMBER WITH "BROWN SPORES."	NUMBER WITH ZYGOTES.	NUMBER WITH SPOROZOÏTES.
April	5	—	—	—
May	169	4	—	—
June	144	8	—	—
July	157	3	1	1
August	107	5	3	2
September	117	3	1	1
October	131	10	22	—

Further, as we shall point out elsewhere, it is not so clear in the tropics that there is a direct dependence between the number of anophelines at any particular time and the intensity of malaria, and, indeed, it would be hard to predict what would be the effect of an increase in anophelines; possibly more may become infected, yet this may be counterbalanced by the increased number also of those not infected.

Disturbance of the Soil.—This is, in my opinion, one of the older epidemiologic observations on which the mosquito cycle does not shed any light. The general explanation given is that this leads to the formation of pools, and so to the breeding of anophelines, and then to the infection of these, though by what previously infected cases it is generally not stated. Now, over and over again have planters, engineers, etc., informed us that working on virgin soil or opening up a jungle was especially a cause of "fever" among laborers or coolies. Moreover, this fever attacked these men *in a few days*, and not some weeks or a month later. That we are dealing here with a factor dependent on anophelines is, I think, extremely doubtful, and, indeed, it is doubtful also whether the so-called "fever" is malaria at all. Until this point has been established it would be useless to attempt an explanation, nor can we attribute much importance to the statements so often made that malaria broke out in certain places coincident with the formation of a few new pools during engineering work. If larvæ are found in these pools, it is evidence that anopheles exist in the neighborhood, and, moreover, if malaria breaks out, the explanation seems to me to lie in the fact that infected *Anophelinæ* also exist in the neighborhood rather than that the pools started the epidemic, though it is, of course, possible that the infection started among the workmen themselves; though in the case of the turning-up of soil mentioned above, frequently the coolies live a mile or so from where they worked, and the pools, if any are made by them, cannot influence the "fever" one way or another.

Malaria Contracted at Night.—This is an old observation, completely in harmony with modern views, and is explained by the nocturnal habits of the anophelines.

Malaria Confined to Certain Houses.—This, which was difficult to explain on the water or miasm views, is, of course, adequately explained by the mosquito cycle. Moreover, we know that anophelines do not travel far in search of food and water, and, in fact, for all we know to the contrary, return to the houses they leave. An infected anopheline in such a house might and often does infect all the inmates. These are a few of the more important epidemiologic facts which the mosquito cycle has been found completely to satisfy, and we may say that there is no *fact* which clashes with the mosquito view or which suggests that there is any further cycle but that in the mosquito.

HABITS OF ANOPHELINÆ.

Influence of Wind and Rain.—There can be little doubt that mosquitos, as other diptera, dislike wind, though we shall consider later exceptional instances where mosquitos are transported long distances by the wind, yet ordinarily when the wind blows, one is free from their visits. Similarly, heavy rain is to their detriment, while slight rain may stir them to activity after a period of drought, and rain may apparently make *Anopheles* more numerous, as they seek shelter from it in houses.

Height of Flight.—That anophelines can fly at a height of 20 feet from the ground as a common occurrence seems probable, as they are found in dwelling-rooms at that height; they have also been observed at a height of 30 feet, but the limit cannot at present be stated.

Estivation.—In the tropics they can probably exist for two months or more in the complete absence of breeding-grounds during the dry season, though very careful observation is necessary before all possible sources of water can be excluded.

Relation to Color and Smell.—The great source of anophelines in the tropics is the native huts of the aborigines. Here they abound in myriads. They, moreover, actually prefer the strong odor of natives, as observations made by Christophers and myself in Sierra Leone showed. We kept a tent under observation; while this was tenanted by a European a few anophelines only were caught, in the morning; when, however, a negro slept in it, on the first morning 19 were caught, on the second, 62; when again the European occupied it, the numbers rapidly fell. Blue serge cloth, it is well known, anophelines and other mosquitos have a special liking for, and yellow cloth they least like, but this may be rather a matter of color than of smell. Leather goods, old boots, etc., seem to exercise a peculiar attraction.

Length of Life.—It was originally supposed that mosquitos, when they had laid their eggs, died. We shall see that this is not so, but that the process can be repeated several times if the mosquitos are properly fed. The observation is, however, probably true of those mosquitos which have hibernated during the winter (in a fecundated state). On the return of spring they sally forth and lay their eggs and die.

Seasonal Prevalence of Anophelinæ.—Our knowledge on this subject is slight. We have seen already that the breeding-grounds of different species may often be different; thus, *M. rossii* breeds in shallow muddy pools in stagnant water, whereas *M. listoni* breeds in fresh stream water. Now, the disappearance of *M. rossii* from certain areas during the dry season is determined by the fact that all these stagnant pools may be completely dried up, and it is not until we eventually reach a village or district having suitable pools that we find this species. So, again, if the streams which held the larvæ of *M. listoni* dry up, then this species becomes scanty or even absent. So, again, the distribution of *Mr. nigerrimus* (and probably *P. superpictus*) is determined almost entirely by the formation of large swampy areas of weedy marsh. We have but few records of this seasonal prevalence in the literature of mosquitos. Thus Theobald quotes a statement to the effect that "*N. prætoriensis* first appeared about February 10, and gradually became more prevalent, superseding the other common species, *P. cinereus.*" Again, "In the winter, up to June, one only sees *C. pipiens*. These then disappear, and *P. chaudoyei* appears."

Hibernation of Anophelinæ.—In temperate climates mosquitos pass the winter in two ways: (1) By hibernation of larvæ; (2) by hibernation of adults. The former condition we have already dealt with. Annett and Dutton have described the finding of *A. maculipennis* in cold cellars and outhouses during the winter, but not in warmer stables. The hibernating insects are all females, and these are always fertilized. If the females are roused from their sluggishness by bringing them into a warm room, they will feed, and after a time lay eggs. If, however, the temperature be kept low, they do not arouse themselves and do not feed. Grassi found, with regard to the hibernation of *A. maculipennis* in Italy, that the insects were most numerous in heated rooms, stables, houses, hen-roosts, outhouses. They begin to disappear about February, and almost completely in March, but, according to Macdonald, in Spain not until May or June. Probably they have aroused and laid their eggs and died. According to Schoo, in Holland the hibernating *Anophelinæ* lay their eggs in February and March, but he states that the infected *Anophelinæ* lay no eggs (how this was determined is not stated), and that the latest new infections occur in October and November. Similarly Thayer has found *A. crucians* and *A. maculipennis* hibernating in enormous numbers in barns in New Orleans. In Europe the winged insects of *A. maculipennis* appear about June. The occurrence of isolated cases of new infections with malaria in Italy during winter and spring is attributed to the agency of these hibernating anophelines. In the early months some of these may fly abroad, as early as February on warm days, and, further, as Koch has pointed out, in thatched houses where anophelines exist the temperature is high enough to allow of development of the parasite in the mosquito. One fact, however, has not been established, that these hibernating anophelines actually do contain sporozoïtes in their glands, and, in fact, according to Schoo, they do not. And Macdonald's observations in Spain were also negative in this respect.* We may mention here incidentally that Macdonald found the percentage of infected anophelines to be 7 per cent. in June and 18 per cent. in July and August.

Time of Feeding.—Though the anophelines, on the whole, are distinctly nocturnal in their habits, yet there are exceptions to this. The time of feeding appears to be chiefly in the early night and at dawn. Some species appear to be particularly active at dawn; thus Christy in Uganda observed that *Ce. squamosa* and *Ce. pharoensis* blackened the roof of his tent at dawn, though none were to be seen on the previous evening. So of *A. bifurcatus,* Blanchard says that "it bites freely at dawn and dusk, but at night practically not at all." In outhouses and shady places *A. bifurcatus* will also bite during the day-time, and there are several observations to show that other species also do so. Thus in Nigeria and Kamerun *Anophelinæ* (? species) have been found biting in the day-time, and *M. rossii* also occasionally does so in India, but these occurrences are exceptional, for Christophers and myself, while capturing *Anophelinæ* in hundreds of native huts in many parts of Africa and India, have never been bitten under these conditions.

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* Suzuki, in Japan, when the temperature of the external air in January was 7° C., caught an anopheline "asleep" in his house. With this he states that he infected himself with malaria.

THE RELATION OF THE ANOPHELINÆ TO MALARIAL ENDEMICITY.

We have already alluded to the fact that, in spite of ignorant assertions to the contrary, no place where malaria is endemic is known where *Anophelinæ* also do not occur. We have pointed out that the converse is not true, viz., that where *Anophelinæ* exist there also malaria is endemic. In fact, many instances to the contrary are known, and some of these, as we shall see, are difficult of explanation. Thus in England malaria is extinct, though the *Anophelinæ* remain especially in the fen district of Norfolk and Cambridge, which was one of the chief endemic foci. We have previously discussed this point. Similar instances are known even in Italy. Thus, according to Celli, Turin was the seat of severe pernicious fevers fifty years ago, while to-day there is no trace of them: a fact no doubt due to increased population and the accompanying drainage and structural alterations found in large towns; and at the present day it would appear doubtful if any large modern town could be found which is itself malarial; for the *Anophelinæ* are not found under such conditions; thus while Rome (the classic instance) is itself absolutely devoid of malaria, it is only on reaching the villages of the Campagna that *Anophelinæ* and malaria coëxist again, and even in tropical towns and cities we rarely find malaria the scourge that it is in villages, in settlements, in the half-savage suburbs. Thus in large cities like Bombay and Calcutta our observations led us to doubt the belief that malaria was contracted in the heart of these, but to the conditions existing in Calcutta especially we shall return later.

Our intention here is to consider more especially the distribution of existing endemic foci and their relation to *Anophelinæ*. Now the data for an exact consideration of this important question are very imperfect. We know, for instance, that malaria has decreased or almost disappeared in Holland and Germany, while even in Italy in the north it has likewise been decreasing, though in the south it is as severe as ever. It is probably true that the west coast of Africa, the Kongo, and the equatorial regions of Africa are the foci of the most severe malaria in the world. The explanation is difficult, and we shall find that, even when we endeavor to explain such great variations as occur within a distance of 50 miles or even 10, we cannot do so completely. To return to Italy: it is well known, and has recently been pointed out again by Schaudinn, that malaria is a mild disease with a trifling mortality in northern Italy, while in the south, in Sicily and Sardinia, it is extremely severe. It is true that the climatic conditions are different here, and, no doubt, whatever this implies, that this is the determining cause; but, as we shall see later, similar differences in endemicity can be found without any recognizable difference in climate. However, climate is obviously a factor, for in the United States the area of severe malaria and blackwater fever is that bounded roughly by the isotherm of 55° F., and the occurrence of malaria in northern Europe is determined by the same factor. How far this also determines the distribution of the *Anophelinæ* it is difficult to say—the data are insufficient. Again and again we find statements in the literature of malaria, even at the present day, in which it is assumed that the finding of *Anophelinæ* is an adequate explanation of the occurrence of malaria anywhere. Rarely do we find that the only proof, viz., the finding of *Anophelinæ* infected with parasites, is forthcoming, for the *Anophelinæ* that have been found may, as we shall show, have nothing to do with the occurrence of malaria, and, as we have repeatedly stated, the finding of *Anophelinæ* is no proof of the existence of malaria in a place, and this is true also of the tropics. Thus in the outskirts of Calcutta, not in the town itself, we have conditions precisely similar to those found in any village in tropical Africa—numerous native huts, a dense population, innumerable *Anophelinæ*, and the necessary breeding-places near at hand. In such surroundings we should expect to find malaria rife, but, as a matter of fact, it is completely absent. Before discussing the causes of this remarkable fact we may first consider what means we adopt to determine the extent to which malaria prevails in any particular place. If we capture a number of *Anophelinæ* in the dwellings of the native population in the tropics, we find that, as a rule, a considerable number of them are infected; that is to say, contain malarial sporozoïtes in their salivary glands. What is the source of this infection of the mosquitos? It is not, as was at first thought, that it is caused by the mosquitos having fed upon isolated cases of "fever" among the population, but it arises from a quite unsuspected source of infection in the native children. The native children are, to all appearances, quite well and not suffering from fever; they run about, attend school, etc., but a microscopic examination reveals the unexpected fact that their blood may contain numerous parasites. It has been urged that this infection of native children was not a new discovery, for it had been found earlier that native children exhibited pigment in their spleen examined postmortem. Though this is so, yet it is quite a different matter to have discovered that practically all the native children apparently healthy, harbor parasites and are capable of infecting mosquitos. This fact, of prime importance in the study of malaria prophylaxis in tropical regions, was announced by Koch, and independently by Christophers and myself in West Africa. *It is the native, in fact, that constitutes the great source of infection of Europeans in the tropics,* and comparable to this the supposed danger arising from a case of European malaria is a mere drop in the

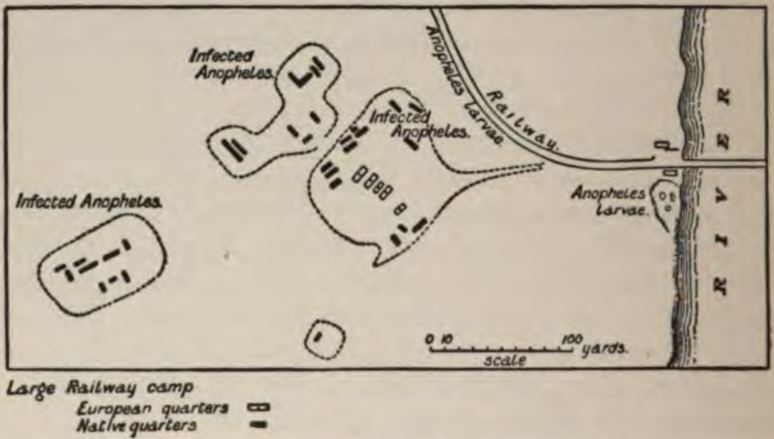

FIG. 9.—SHOWING HOW EUROPEANS ARE INFECTED WITH MALARIA FROM THE NATIVE CHILDREN (from Stephens and Christophers' "Practical Study of Malaria").

ocean. We say supposed, because it is a peculiar fact that in many cases gametes are absent in the blood of Europeans in the tropics, though they may readily appear on return to temperate climes. Natives, then, are the great source of malarial infection in the tropics. How, then, can we estimate the extent to which malaria prevails among the natives? We have a ready and simple test. If the blood of a number of native children be examined, it will be found that the number of those containing parasites varies according to their age, and that beyond a certain age the percentage of those infected becomes very small. Thus in a village examined by us in West Africa, of the babies, 90 per cent. contained parasites. Children up to eight years, 57 per cent.; up to twelve years, 28 per cent.; over twelve years, rarely infected. For a good practical test the age limit of ten years may be taken, and the parasite rate of the children below this estimated. Of course, as far as possible, children of the same age should be examined when comparisons are made of the malaria in two different localities. The percentage of infected children under ten years of age we have termed the *endemic index*, and we have in the different values of this for different localities an accurate test of the extent to which malaria prevails, or, in other words, of the *malarial endemicity*, as we termed it. To return, now, to the conditions we found in the outskirts of Calcutta. Under the conditions we have described above we expected to find a high endemic index among the native children, but to our great astonishment it was nil. Some hundreds of children were examined in the outlying villages, but uniformly with the same result; we never found one containing parasites, though examinations were made in different districts, and during the months believed by all to be those of severest fever. Now, the native dwellings in these districts contained thousands of *Anophelinæ*, and they could be found breeding in astonishing numbers everywhere. We further dissected over 300 *Anophelinæ* captured in these huts, but likewise none of them were infected with sporozoïtes. The suspicion consequently arose that possibly these particular *Anophelinæ* did not transmit malaria, and certain investigations that were subsequently made confirmed our view. Now in Calcutta, the predominant species was *Myzomyia rossii*, and although, as we shall see, it is unsafe to assume that the anopheline most easily found is the carrier of malaria, yet careful *personal* search convinced us that this was the species always present, and often only this. At any rate, it was certain that here there was no malaria to transmit, for the children were all free from it. This, then, was the unexpected condition in Calcutta, viz., an edemic index of 0. We then travelled up country some hundreds of miles from Calcutta and proceeded to examine in the same way the native children.

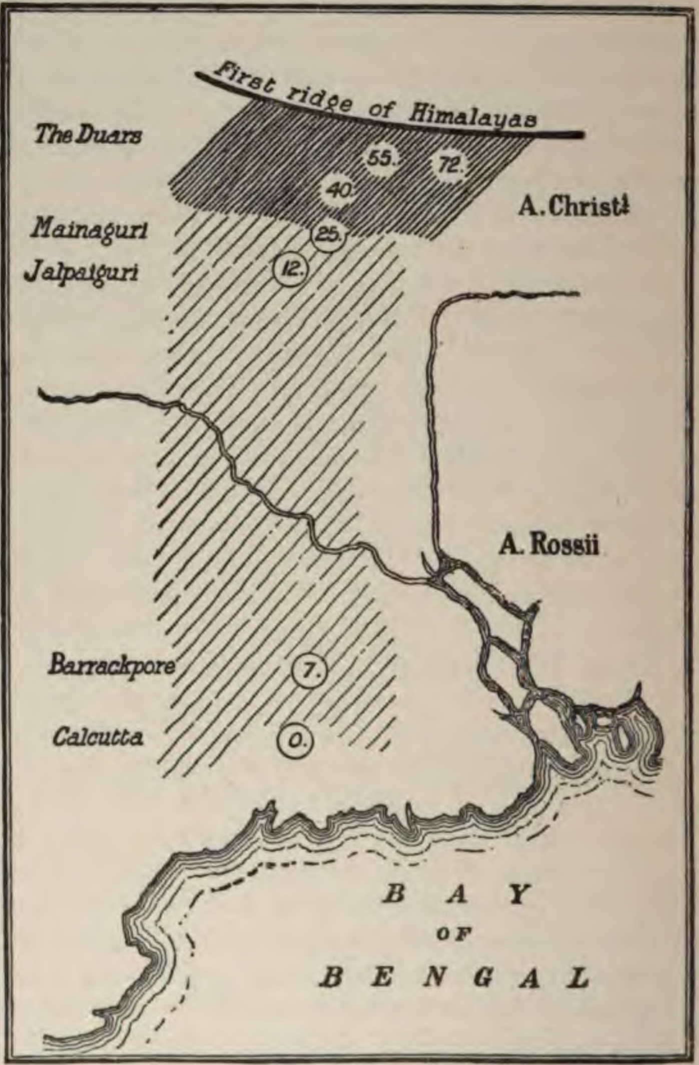

FIG. 10.—SHOWING VARIATIONS IN MALARIAL ENDEMICITY (from Stephens and Christophers' "Practical Study of Malaria").

Here the endemic index was 12, remarkably low compared with 70 per cent. to 80 per cent., a common figure in West African children; and it was only on reaching the foot of the Himalayas that we found the condition of things parallel to what we had previously found in Africa. Here the endemic index ranged from 55 per cent. to 72 per cent. in two villages examined by us. How, then, can we explain this change from 0 to 72 in a region where, so far as we could judge, the climate and other conditions were the same? There was, however, one important point in which these districts differed. Whereas *M. rossii* was the prevailing anopheline at Calcutta, it was not so at the foot of the Himalayas: here the prevailing anopheline was *M. listoni*, and, moreover, dissection showed us that this species was the carrier of malaria here. It seems, then, that the difference in malarial endemicity had to do with a difference in the species of *Anophelinæ*, and, in fact, we were able to prove this later in quite a different way. We argued if this idea were correct, that when we found the two species together, one would be infected and the other not. When, then, the opportunity arose, we proceeded to put the matter to the test by dissection. The two species (in this case *M. culicifacies* and not *M. listoni*) were captured under identical conditions—that is, they were caught in the same house, in the same village, at the same time. The following table gives the results of our dissections made in two widely distant districts:

MIAN MIR (PANJAB).

	Number Dissected.	Number with Sporozoïtes.	Percentage with Sporozoïtes.
M. culicifacies	259	12	4.6
M. rossii	496	0	0
	ENNUR (MADRAS).		
M. culicifacies	69	6	8.6
M. rossii	364	0	0

So that here, under conditions where *M. culicifacies* was transmitting malaria, *M. rossii* was not. The result of the experiment was thus of the greatest importance, showing that all *Anophelinæ* do not transmit malaria, or at least in these two instances *M. rossii* did not. Further dissections of *M. rossii* have all proved so far negative, and although this species abounds in tropical towns, such as parts of Madras, Calcutta, and Bombay, there is no reason to suppose that it can convey malaria in nature. In experiments it is not the same, for by feeding *M. rossii* on infected cases, it was found to carry malaria, though perhaps not so readily as other species; and before we consider here the bearing of this question of species on malaria endemicity, it will be well to mention here that similar results to ours in India have recently been gotten in the United States. Thus

Hirshberg made a series of comparative experiments by feeding *A. maculipennis* and *A. punctipennis* respectively on the same cases of malignant tertian malaria, placing each species under the same conditions. The two species were kept in the incubator at 30° C. Under these conditions sporozoïtes developed in eight days. Out of 58 *A. punctipennis*, none developed sporozoïtes, while out of 48 *A. maculipennis*, 8 were positive. It is very evident then that the species of anopheline is a most important factor, and in all probability it will be found that in nature also *A. punctipennis* does not carry malaria, but we would again observe that this is a point that must not be assumed, but decided by actual dissections of this species caught in houses where malaria prevails. If we may venture to draw conclusions from a single series of experiments, we should be inclined to think that here also *A. maculipennis* was not a particularly good carrier as compared with tropical species, but the number of times that the mosquitos were infected by feeding may be the explanation of this. Of the actual cause of this difference in carrying power of two species of the same genus we have at present no explanation. This is one aspect of the importance of species, but we must consider another phenomenon which is equally peculiar. We have already noted the disappearance of malaria from districts where it formerly prevailed, and have noted the explanations generally given for this fact, but the following instances will show that we can have *all* (?) the conditions necessary for the appearance of malaria in a tropical country, and yet a complete absence of malaria. Thus in a district of Madras investigated by Christophers and myself in India we found in two villages, about a mile apart, with the usual teeming native population, myriads of anophelines and numerous breeding-places,—and, moreover, here the anopheline present was *M. culicifacies*, one which we knew to be an efficient carrier of malaria,—that an examination of the blood of the native children showed that they were completely free from parasites. The possibility of the introduction of malaria into these villages, if we must suppose this necessary, was a daily occurring one, for the villages were the halting stages of the large traffic passing up and down the country. Malaria was rife in the district, moreover, and 15 miles away, at an elevation of 1000 feet, the endemic index was 50. These are instances of what Celli has termed *Paludismus sine malaria*. A minute examination of these villages and the conditions prevailing there failed to give us any clue as to the explanation of this remarkable condition. In the light of so exceptional a condition in a malarial district we think that the explanations usually given for the disappearance of malaria from a given spot are inadequate. While giving their due importance to these exceptional cases, we must not overlook the very close relationship between the distribution of the *Anophelinæ* and endemic malaria, and yet, while we can establish this, we shall find that in considering even this normal relationship we encounter peculiarities in the endemicity or malarial index of localities that we cannot at present explain. In endeavoring, then, to elucidate the factors responsible for the varying endemic index in different parts of India, Christophers and myself selected a number of villages, isolated, but all within a circle of about 10 miles in diameter. Our method was to determine the endemic index of each village, and, at the same time, the species of *Anophelinæ* caught in the native huts, to map out accurately every breeding-place, actual and potential, and the larvæ found there, to note what breeding-places had dried up, and, in fact, to determine, as exhaustively as possible, every factor that could possibly influence the endemic index. We examined in this way 10 villages. The differences in the endemic index were striking, varying from 45 per cent. to 5 per cent. The differences depended on *one* factor, the presence or absence of *Anophelinæ* in the native huts, and this depended directly on another factor, the presence or absence of breeding-grounds. Thus, to take two examples: in the first case, where the endemic index was 45, anophelines were caught with ease in the huts (and among them *M. culicifacies*), and their breeding-grounds were only a few yards away, whereas where the endemic index was only 5, no anophelines were found by careful search in the huts, and there were no breeding-grounds nearer than half a mile. It is, perhaps, necessary to explain how the endemic index was 5 and not zero where no *Anophelinæ* existed, but this is due to a residual infection persisting after the rainy season, when throughout the country it would be possible for *Anophelinæ* to breed in many places.

These observations then showed us that an almost exact parallelism existed between the presence of Anophelinæ and distance of breeding-grounds, and the value of the endemic index, and we would mention here, incidentally, a conclusion that resulted from these observations, viz., that a distance of half a mile to a mile from breeding-grounds was sufficient to place a village in a zone free from malaria; in other words, that *Anophelinæ* did not, under these circumstances fly more than a half a mile or one mile. While, then, our observations show an almost exact parallelism between the existence of

Anophelinæ (and their breeding-places) and the existence of malaria, yet on examining the figures closely and comparing them with others obtained elsewhere facts difficult of explanation presented themselves. Thus in the district where 10 villages were examined, nowhere did the endemic index exceed 45, while in some it was as low as 5. How, then, is one to explain this comparatively low intensity when we compare it with that of another 10 villages examined in Madras (Jeypore), where the endemic index was almost uniformly high, not sinking below 20 and reaching as high as 86; and, indeed, the difficulty of explaining these variations became even greater, when, as in this latter case, the comparison was made with another series of eight villages distant only some 30 miles from the former, where the climatic conditions were identical. In these latter villages four were found where the endemic index was zero and the highest figure reached was 27. Of these facts no explanation is at present forthcoming. To climatic differences are generally assigned the differences between the mild malaria of northern Italy and the severe malaria of southern Italy, but these instances we have just adduced occur where the explanation, so to call it, of climate would hardly suffice. What factor is it, for instance, that makes the malaria of West Africa the most severe form we know? That malaria is a virulent disease in some countries and a mild one in others has often been overlooked. Why is it that blackwater fever dependent on malaria is practically coterminous with severe malaria, but even then not always? Why, again, is the west coast of Africa the home *par excellence* of the malignant tertian parasite, so that in a European returning from there, in 99 out of 100 cases, it is this parasite that is present, while in Europeans returning from the West Indies and South America it is the simple tertian that is most commonly found? Why, again, in certain parts of India, in the tea-gardens of the Duars, is the parasite in the native children exclusively quartan, while in Lahore (Panjab) it is almost entirely simple tertian? These and many other similar questions we cannot at present explain; we have, however, said enough to make it clear that before these problems can be solved far more precise knowledge of endemic malaria and the accompanying *Anophelinæ* will have to be acquired. The "regional factor," an expression used by Christophers and myself to embrace these unknown causes, must be elucidated, and we shall then be enabled to construct maps of malarial distribution having some more definite value than those dubiously shaded examples which we at present possess.

TECHNIC.

Capture of Anophelinæ.—This can be effected in two ways: (1) By capture of the winged insects; (2) by breeding out from larvæ and nymphæ. Nothing less than personal investigation will suffice to give an accurate idea of the distribution of *Anophelinæ*. Search must be made in the huts of the aborigines in the tropics: the darkest corners of the hut must be carefully scanned, and soot and cobwebs must be braved if *Anophelinæ* are to be detected. Cow-sheds, outhouses, stables, the eaves of huts, all should be searched. The most certain way of detecting mosquitos in thatch, where they are often difficult to see, is to prod it with a stick, when the mosquitos, if present, at once fly out. The mosquitos are captured by very slowly placing a specimen tube, about half an inch in diameter, over them. The orifice is plugged with wool, and the mosquito is transferred to a dry bottle also plugged with wool. *Anophelinæ* may sometimes be found in loose hay or dried grass stored in outhouses, in astonishing numbers.

Capture of Larvæ.—Larvæ must be sought in every possible source of water. It must never be taken for granted that any source of water, however unlikely, is free from *Anophelinæ*. Inspection is not sufficient. Dipping alone will prove the absence or presence of larvæ. For this purpose an enameled cup or tin mug is the most convenient apparatus; a net or other device is seldom necessary. The cup is dipped suddenly into the water, and weeds, débris, and water are all brought up together. Then allow a little time to elapse —the larvæ or pupæ come to the top. They are best lifted out with a teaspoon and placed in the collecting vessel or tube containing water.

Breeding Out Mosquitos.—Place the larvæ or pupæ in a jar or wide-mouthed bottle half full of water. Cover with a lid, the central portion of which is replaced by netting. By naked-eye inspection and more exactly by examining under the microscope, as previously described, the various species may be separated. Place the bottle in a good light, but the water must not become too hot. Remove the pupæ as they develop, and place in separate jars. If larvæ are raised from the egg, it is necessary to provide them in the laboratory with plenty of food, such as they get in nature, and to see that they are frequently supplied with natural water and weeds, otherwise their development is extremely slow.

Mounting of Mosquitos.—As the winged insects hatch out, slip a piece of paper under the lid and place the lid on the table with the paper uppermost. Then place a glass jar over it and remove the paper. The anophelines are then inside the jar, and may be killed with chloroform, tobacco, or cyanid. Some few hours should be allowed to elapse before killing anophelines after they have hatched, in order to allow of their wings hardening. After killing, place the mosquito on a clean sheet of paper. Turn it over with a pin on its back. Previously pierce a card-board disk about as big as a silver quarter-dollar with a fine silver entomologic pin (No. 1). Then pass the pin into the thorax of the mosquito, in the region of the legs, causing it to emerge on the dorsum. Now lift the transfixed mosquito and push the pin a little further through by pressing against a piece of cork or tissue-paper, so as to damage the scales as little as possible. The mosquito is now mounted on the disk. Now transfix the disk at the edge with an ordinary stout pin, passing it in the opposite direction to the fine silver pin. The legs and wings may then be arranged symmetrically, using a pin only for touching the mosquito. Finally place the specimen in a collecting box or pin on to a cork, and insert the cork into a specimen tube; the mosquito is thus inside, and is protected from dust and damp, and, should injury befall it, all the parts will be still preserved inside the tube.

Keeping Mosquitos Alive.—Mosquitos other than the anophelines can be kept alive by feeding on fruit-juices, such as bananas, dates, sugary water containing a little sherry, etc., and it is noteworthy that mosquitos will often live longer in a closed jar, even when corked, than in a cage covered with netting. From a considerable experience with anophelines in feeding experiments in the tropics Christophers and myself found it advisable not to use a cage, but to keep our mosquitos in bottles. One of the most convenient methods is to use a bottle with a hollow stopper into which some water is placed. The jar is inverted, and a piece of cork is placed on the water; on the cork is placed a piece of white paper. This serves as a resting-place for the mosquitos during oviposition. Further, a piece of card-board is forced into the jar, so that it rests on the neck inside. This serves as a support for the mosquitos to rest upon. Such a jar is ready for feeding experiments.

Feeding Anophelines on the Blood of Patients.—The jar, prepared as above, has the stopper removed; it is then placed above the vessel in which the insects have hatched out, and the mosquitos transferred from the latter to the former. A piece of mosquito netting is next tied over the mouth, and the jar is ready. According to various observers, twenty-four hours must elapse before the mosquitos are ready to bite after they have been hatched. Twenty to thirty mosquitos are used for the experiment, which is begun about dusk or later. The arm of the patient is now firmly applied over the mouth of the jar, and it will be found that the mosquitos will bite readily through the netting. Allow all the mosquitos to feed. If the mosquitos are hungry, splashes of blood passed per anum will be seen on the sides of the bottle. After feeding, remove the netting and replace the stopper, and place in an incubator at about 80° F. Any mosquitos, *e. g.*, males, that are found dead next day may be removed, and eggs that have been laid may be collected. Fresh water should be supplied every morning. The bottle should be labeled, and the time of feeding, etc., carefully noted on the label.

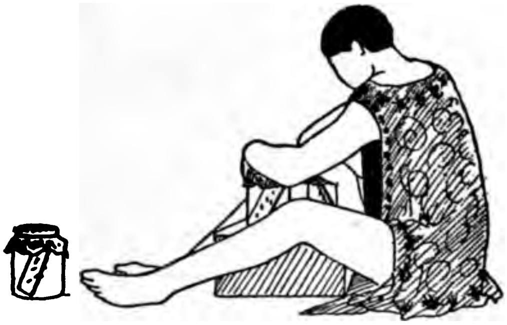

FIG. 11.—METHOD OF FEEDING MOSQUITOS (from Stephens and Christophers' "Practical Study of Malaria").

To Examine Fed Mosquitos.—Place the bottle containing the mosquitos aside, or capture as many as required and place in another bottle. Keep them in the incubator until they have digested all their meal of blood; this is known by the complete disappearance of the black contents of the stomach and by the feces becoming white. Mosquitos containing undigested blood in their stomachs are difficult to dissect, and unsatisfactory results will be obtained unless this precaution is taken.

Dissection of Mosquitos.—(A) *Isolation of the Salivary Glands.*—It is convenient to remove the legs and wings. The anopheline is then placed in a drop of salt solution,—0.5 per cent. suffices,—lying on its right side with the head facing the dissector. A needle is placed on the thorax to steady the mosquito; with the other needle in the right hand, steady *gentle* traction is then made on the head, placing the needle just behind the head or slightly on the neck. By gentle pulling the head is removed, together with a little whitish mass of tissue in which the glands will be found. The dissection, which up to this stage is best done on a white surface, is now best done on a dull black surface. If the whitish mass of tissue has come out from the thorax, examine with a lower power of the microscope (½ inch) for the glands. The glands are seen as *glistening*, finger-like processes. The head is again steadied with the needle, and a transverse cut is made between the glands and the head with the other needle.

Examine again under the microscope to see if present. They may then be further teased out if necessary. As a rule, all six lobes are got with ease and certainty by this method. If, however, they have not been drawn out, they will be found still lying just near the attachment of the first pair of legs, and this position of the thorax is then isolated by dissection.

The glands are now transferred with a needle to a clean drop of salt solution, a cover-glass is applied, slight pressure made, and the examination made for sporozoïtes with a ⅐-inch lens.

Bodies are sometimes met with in the glands of *Culex spp.* (and *Anopheles*) which resemble sporozoïtes, but do not, on staining, show a nucleus. Crystals are found also in the glands, which have some resemblance to sporozoïtes. Further care should be taken not to mistake in fresh preparations the wrinkled appearance of the esophageal diverticula for sporozoïtes. Pseudosporozoïtes, as Grassi calls them, have been found by him in *A. maculipennis.* They are shorter than true sporozoïtes—they are about 5 to 10 μ—and do not stain characteristically. He supposes them to be products of the glandular reaction. They probably correspond to the crystals found by Christophers and myself in African anophelines.

(B) *Isolation of the Midgut.*—The mosquito from which the glands have been removed can still be used for examining the viscera. The mosquito is placed on its back, and with the needle a nick is made on either side in the chitinous exoskeleton near the hind end. One needle is placed on the thorax to fix it, and traction is made on the separated hind segment. If the dissection is made on a dark surface, the viscera will now be seen—midgut, Malpighian tubes, and ovaries. The esophagus and its diverticula will also possibly be seen, or they may have been extracted in the previous dissection. The anterior end of the midgut is cut across and the Malpighian tubes and ovaries may also be removed. A cover-glass is applied; slight pressure then causes the "stomach" to flatten out, and zygotes, if present, can readily be seen with a one-sixth inch lens or lower power. To preserve fresh preparations the specimen is irrigated with 2 per cent. formalin solution or surrounded with glycerin; the latter gradually mixes with the fluid in which the dissection has been made, and the specimens are finally ringed with zinc white or other cement.

To Make Permanent Preparations of Sporozoïtes, Zygotes, etc.—If sporozoïtes have been found in the fresh preparation, the cover-glass is "smeared" off carefully and the slide and cover-glass are then dried as rapidly as possible. Fix the specimens in alcohol and stain with the Romanowsky stain. (The Romanowsky stain is made in the following way: Pure methylene-blue, 1 part; carbonate of soda, 0.5 part; water, 100 parts. Keep in the sun or incubator until distinctly red. A second stock solution is made, consisting of eosin (yellowish, pure, soluble in water), 1 part; water, 1000 parts. For using, dilute each stock solution 20 times with water and mix equal parts of the dilute stains. Stain for ten minutes or longer; wash in water. Dry without using heat.)

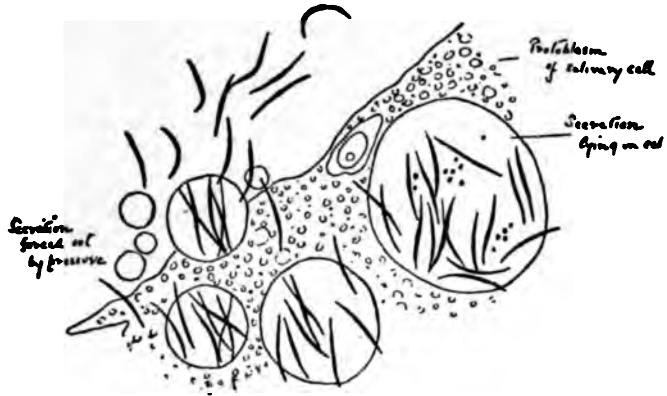

FIG. 12.—SPOROZOÏTES IN THE SALIVARY GLANDS OF AN ANOPHELINE (FRESH PREPARATION) (from Stephens and Christophers' "Practical Study of Malaria").

Staining Zygotes.—When found, float the cover-glass off carefully and allow the stomach to flatten out on the slide as completely as possible. Drain off the excess of solution. Dry and fix. Stain with hematein solution: Hematein, saturated solution in 70 per cent. alcohol, 10 c.c.; alum solution (alum, 50 grams, water, 1000 c.c.) 250 c.c. The solution improves with keeping. As ordinarily performed, satisfactory results cannot be obtained with the Romanowsky stain owing to the non-penetration of the stain through the cyst-wall, and further to the fact that it is generally advisable to dehydrate the specimen with alcohol. But the following modification of Christophers may be used. Stain for ten to fifteen minutes with the stock eosin solution; pour off the excess, and press with blotting-paper. Then stain with the diluted methylene-blue solution for fifteen to twenty minutes. Pour off excess and wash rapidly in 70 per cent. alcohol; transfer immediately to water. If the tissue is dark purple or blue, wash in dilute acetic acid (1 : 400 water). If the tissue is, however, light purple or light reddish, omit this. Allow the tissue to dry upon the slide.

To Cut Sections of Mosquitos.—Remove the limbs and wings and make an incision with a razor through the chitinous covering of the abdomen and thorax to allow thorough penetration of the fixing fluids. The mosquitos are, in the first place, best killed by dropping direct into absolute alcohol. Boiling the mosquitos in absolute alcohol is recommended by some authors. The mosquito is then embedded in the usual way in paraffin or celloidin.

To Cut Sections of the Salivary Glands.—Only the head and front half of the thorax need be taken. Cut sections horizontally.

GENERAL SYMPTOMATOLOGY.

THE FEVER.

The most constant and dominating symptom in the clinical picture of malaria is the fever. The great attention always bestowed on this symptom and the readiness by which it could be proved resulted in its being made the base of classification of the different clinical forms.

Yet the course of the fever in malaria shows such wide deviations —from curves of mathematic regularity to curves of complete irregularity—and sudden changes that the classification could be only a forced one. Moreover, it may not at all correspond to the general severity of the attack.

The association of the fever with the other symptoms in this classification gradually produced numerous forms and categories, until Dutrouleau's expression, "C'est le chaos," seemed entirely justified.

In our opinion, neither the fever nor any other one symptom can be made the base of a classification of the malarial diseases, for the simple reason that the form of the fever and the severity of the infection do not correspond. As an illustration, let us take quotidian fever. It would be a great error to put two such cases under one head, on account of the similarity of the fever; for one case might be caused by a plural infection with quartan parasites, the other by an infection with the small pernicious parasites. The whole consideration of these two cases from an epidemiologic, clinical, prognostic, and even therapeutic standpoint would, therefore, be different. In all confidence, therefore, we plead for a new rational classification on the basis of the species of parasite which causes the infection. How this is to be carried out will be seen in the special part of this treatise.

Returning now to the symptom of fever, we may say, first, that it is extremely exceptional for a malarial infection to run its course from beginning to end without any elevation of temperature, though, on the other hand, during the course of the infection, long apyretic intervals may occur, so that it is not justifiable to conclude that the disease has terminated on account of the temporary absence of pyrexia.

Observing the forms of fever, we find that all known types occur: remittent, intermittent, and continued. Moreover, these types may occasionally alternate in the course of the same disease, and an intermittent may prove regular or irregular.

The regular intermittent fever occurs so rarely in connection with other diseases, and is so common to certain malarial infections, that it has stamped itself on malaria and lent it its name, intermittent fever.

We distinguish a quotidian fever when a paroxysm occurs daily, a tertian fever when there is an interval of one day between two fever days, and a quartan fever when there is an interval of two days. In addition to these common types there are others, as the double quartan, with a paroxysm on two days following each other, then a day interval; triple quartan, double tertian with daily paroxysms; duplicate quotidian fever,* with two paroxysms on one day, etc. These designations take into consideration the causal factors of the fevers, which, from a general pathologic standpoint, would be regarded only as quotidian fevers.

Intermittent malarial fevers with long intervals, as, for instance, septan fever, have been observed by Kelsch and Kiener in Algiers, by Borius, Thaly, and Mahé in Sénégal, by Laure in Guiana, by Gelineau on Mayotta Island, and others. As will be shown in the section on Relapses, these fevers are not to be regarded as particular types caused by specific species of parasites, but as relapses occurring with a certain regularity.

The intermittent types may be regular and show corresponding curves, or they may manifest certain irregularities. Among these irregularities we may mention, first, anticipation and postponement of the paroxysm, in that this may occur a few hours before twenty-four (or forty-eight or seventy-two) hours, or a short time after the regular interval. The former is much more frequently observed. The postponing type is usually the result of quinin treatment and precedes recovery.

Another form of irregularity consists in the change of type; for instance, a quotidian after several tertian paroxysms, or vice versâ.

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* We differentiate, with Sauvage, a febris duplicata or triplicata from a febris duplex or triplex; by the former we understand the occurrence of two or three paroxysms on one and the same day; by the latter, the occurrence of two or three paroxysms on different days. Further details will be found in the Special Part.

The quartan type may also alternate with the quotidian. A change from tertian to quartan by postponement, as described (doubtless theoretically) by older writers, does not occur; at least, I have never succeeded in finding a convincing example. The explanation of this limitation of the change of type will be found under Special Remarks.

Finally, there is an irregular intermittent fever, occurring especially in connection with quotidian and tertian, in which the well-known characteristics can no longer be recognized through the irregularities, and an apparently arbitrary form is assumed. By remittent fever we understand a subclassification of continued. The difference is that in remittent the temperature now and then falls almost to normal, while in continued it remains at approximately the same level.

It is customary, too, to designate the remittent of malaria as subcontinued or subintrant (or subingrediens). The remissions may show a regularity by recurring at definite intervals and to the same degree. This form is not uncommon, and may be produced by a prolongation of the individual paroxysms, by anticipation, or by increase of the paroxysms within a definite interval. Several factors often act together. In these cases, therefore, the second paroxysm sets in before the first one has fully terminated.

Some writers differentiate between subintrant (seu subingrediens) and subcontinued. In this case the name subintrant is applied to that continued or remittent fever which arises by prolongation and anticipation of the paroxysm, the expression being limited to benign fevers. (See Special Part, Div. 1.) This is the benigna continuitas of Torti. The name subcontinua is applied, for instance, by Baccelli, to the continued fevers that arise by the increase of the paroxysms in the course of twenty-four hours. Torti understands by subcontinua a fever that was at the same time continuous and malignant. We consider it unnecessary to complicate the matter to such an extent; and, as will be shown later on, it is often impossible to make such differentiations. After several days, remittent, as a rule, goes into intermittent.

In reference to the pure continued, it is only necessary to say that it usually lasts but a few days, and then, by crisis or by becoming remittent or intermittent, proceeds to recovery or death.

We have at our disposal only a very small number of intact curves of remittent and continued fevers, for the reason that these diseases are frequently dangerous from the beginning, and the administration of quinin must be begun as soon as the condition is recognized; thus, in the majority of cases, breaking up the fever.

Any one of the foregoing types of fever may be manifest throughout an attack, though they frequently combine, thereby producing a great variety of fever-curves, which may confuse the physician who is accustomed to see only the simple forms, as they occur, for instance, in central and northern Europe.*

The temperature may reach a considerable height (hyperpyrexia) —41° C. (105.8° F.) and over is not rare. Subnormal temperatures are also seen, especially in the algid forms. Guéguen once observed in such a case a temperature of 33.4° C. (92.1° F.).

The fever paroxysm, with its three classic divisions, chill, fever, and sweating, is especially common to malaria; though in the severe genuine quotidian, remittent, and continued fevers, it may be entirely wanting or be only suggested. This fever paroxysm is not at all peculiar to malaria, since it occurs very frequently in other infections, as ephemera, influenza, sepsis, and at the beginning of all acute infections. Yet in connection with the other symptoms of the disease it often is a characteristic in the diagnosis.

Mild prodromal symptoms, as malaise, headache, yawning, loss of appetite, eructation, etc., usually precede the fever paroxysm by one or more days. The chill usually sets in suddenly, with greater or less violence. Its severity may vary between a light tremor and the most violent shaking and chattering of the teeth, sufficient sometimes to break them. Patients have not always the sensation of cold, and then appear so only from the forcible shaking, though this feeling is usual, and they bury themselves under numerous covers to become warm, and crouch together in order to lessen the general surface of the body. The condition is often rendered worse by headache, nausea, and vomiting. Objectively the pallor of the skin and the coldness of the extremities are striking. Cutis anserina is frequent. The lips are livid, as are, likewise, the nails; the face is anxious; the pulse is small, hard, and rapid; the breathing is superficial, hastened, frequently dyspneic, and disturbed by the impulsive tremors in which the diaphragm also participates. Senac first made the observation that the mouth temperature did not sink during the chill; de Haen discovered the important fact that it was even elevated, and Gavarret showed that this rise began sometimes before the chill. The skin of the patient is not always cold; in fact, it is sometimes warm; yet, as Lorain has shown, the superficial chilling may proceed so far that the mucous membrane of the mouth and of the rectum feel cool.

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* For the sake of completeness we will mention several types which were constructed rather than observed by old writers. These are mentioned to-day only out of respect for the old names. Among these belong: Amphimerina—continued quotidian; triaeohya (syn. semitertiana, hemitritaeus) = continued + tertian; tetartophya = continued + quartan.

After the chill has passed the patient begins to feel somewhat better, yet this euphoria is transitory and is soon supplanted by a burning heat. This stage is usually more bearable for the patient than the chill. Subjectively, in addition to the feeling of heat, there occur burning sensations in the eyes, thirst, and a throbbing in the head. The face of the patient is flushed, the conjunctivæ are injected, the pulse is full, soft, and often markedly dicrotic. During this stage the temperature rises to its acme, frequently reaching 41° C. (105.8° F.). A rapid decline usually follows, during which the third stage appears. The sweating is sometimes trifling; yet more often abundant, so that the patient must change his linen over and over again. It has sometimes a peculiar, sperm-like, characteristic odor. At this time the patient feels tired and exhausted, but otherwise in a condition of euphoria. The temperature has in the mean time dropped considerably, and the pulse is often retarded. All three stages may be individually or together abortive. The hot stage is wanting most frequently, and if, at the same time, the chill was slight, the patient may overlook the paroxysm and deny its occurrence, though the thermometer would possibly have shown over 39° C. (102.2° F.).

The assertions, therefore, of the majority of patients, when they are not confirmed by the thermometer, are not to be trusted. Positive results are obtained only by the regular taking of the temperature every two hours.

The older writers mention a typus inversus by which they understood a reversal of these symptoms—that is, first, sweating; then fever; and finally the chill. I have never seen such an occurrence, and in more recent communications I have found nothing further in relation to it. It seems to me, therefore, that this "type" was theoretically constructed, and not the result of observation. The so-called "febris dissecta"—that is, with an interval between the three stages—I have likewise never observed, and doubt its occurrence. The duration of the whole paroxysm is variable, and may fluctuate between four and forty-eight hours. Corresponding to this, the paroxysms are divided into short, moderately long, and long. Laveran, for instance, reckons the paroxysms of four to eight hours' duration among the short; of eight to twelve, among the moderately long; and over this, among the long. The duration of the paroxysm is closely connected with the evolution of the parasite, and will be considered in its proper section.

Lorain, who deserves credit for his thermometry of malarial fever, determines the relation of the three stages to one another in the figures 3 : 2 : 7. The longer the paroxysm lasts, the longer is the hot stage, though its period is always the shortest. Griesinger reports the rare occurrence of paroxysms extending over three days, in which the chill occupied the first day, the other two stages the second and the third.

The configuration of the fever-curve, as might be judged, is not always the same. In short paroxysms the curve runs to a point; in long ones we see more or less extended levels. Moreover, the curve does not always show a straight rise and fall, though this may be characterized typical; the decline is not frequently interrupted by a new rise, which may even be followed by a second and a third before the final critical fall occurs.

To determine the beginning of the paroxysm the thermometer is necessary, because the chill, in a large majority of cases, breaks out one to several hours afterward. The assertions of the patients, therefore, as little as they are to be depended upon in relation to the time of the chill, are even less trustworthy for the accurate determination of the beginning of the paroxysm. This can be learned only by the rise in temperature.

According to Maillot and the majority of observers since him, most paroxysms (about two-thirds of all cases) occur between midnight and midday—in other words, in the morning. Moreover, according to Maillot, the greatest number of quotidian and tertian paroxysms occur about 10 A. M.; the smallest number, between 9 P. M. and midnight.

In my experience of 107 cases 91 per cent. of the paroxysms (from the standpoint of the commencement of the temperature-rise) occurred during the period between 10 A. M. and 3 P. M.; in 6 cases the paroxysms occurred early in the morning; in 5 in the evening, and only in 3 between 10 P. M. and midnight. My experience, therefore, corresponds to Maillot's. Maurel observed in Guiana the majority of paroxysms between 2 and 5 P. M.

ENLARGEMENT OF THE SPLEEN.

Enlargement of the spleen is the second most important clinical symptom of malarial infection. In regard to its frequency, writers are by no means unanimous. While some have scarcely ever missed it (for instance, Laveran), others assert that they have often seen cases without it, for instance, Plehn.* Even more those thoroughly grounded students of malaria, Kelsch and Kiener, write† that in simple intermittent fever "aucune tuméfaction de la rate ni du foie n'est appréciable." These last further affirm that they have seldom observed enlargement of the spleen on the first occurrence of a remittent, in contrast to the remittent and adynamic typhoid malaria, in which, from the beginning, a painful tumor of the spleen is usually evident.

Among 132 cases of malaria of different types—cachexias omitted—I have missed only once the tumor of the spleen, and this in a case of severe typhoid malaria with small parasites. Fifteen times the spleen was enlarged to percussion; 116 times it was palpable. It was regarded as enlarged by percussion only when the splenic dulness reached or overstepped the anterior axillary line.

Among my cases there were many primary infections of short duration, as well as numerous relapses. In almost all cases the malaria was verified by the blood examination. This difference in results cannot be fully explained. Omitting errors in diagnosis, which are frequent in malarial as well as non-malarial regions, when the diagnosis is made without a blood examination and with careless examinations of the spleen, there is left little else to which we can attribute this astounding variance. Individual circumstances—like thickening of the capsule of the spleen, which prevents enlargement of the organ—are probably no more frequent than we see them here. A difference in the character of the virus only remains, though this assumption, in the light of the similarity of other symptoms, is not very probable.

From my own experience I can only say that the enlargement of the spleen is a constant symptom in all forms of malarial infection, being in the minority of cases—about 12 per cent.—evident only to percussion; in the majority—about 88 per cent.—palpable.

The longer the disease lasts and the more frequent the infection, the larger and harder becomes the tumor. In a case of recent infection the spleen is soft, has a sharp margin, and extends beyond the arch of the ribs on deep inspiration only one to two finger-breadths. It is a fact, easily confirmed in recent infections, that the spleen increases in size with the paroxysm and becomes smaller during the intervals.

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* "Malarial Fever in Kamerun."

† *Loc. cit.*, p. 446.

According to Griesinger, a whizzing murmur, similar to the placental râle, is sometimes audible over the tumor.

The most marked tumors of the spleen are found in inhabitants of severe malarial regions, who year out and year in are exposed to the infection, and are, as a consequence, in a condition of malarial cachexia.

After one not too prolonged infection, the enlargement may decrease, so as to leave the organ normal, yet this is not constant, for we frequently see the splenic tumor, even though somewhat reduced in size, continue throughout life. This "ague-cake" is more likely to remain the more frequent the infection.

In recent infections the spleen is not rarely the seat of spontaneous pain of a pricking character, which increases on movement of the diaphragm and recalls the pain of pleurisy. In these cases palpation of the organ is very painful. At other times the pain occurs only on palpation.

This pain is usually due to stretching of the capsule, yet it may be due to inflammation of the covering of the spleen; in other words, perisplenitis. The old "ague-cakes"—omitting complications—are usually insensitive.

The tension of the spleen may be so great as to produce rupture of the organ. This occurs especially after trauma and causes almost immediate death on account of the rapid hemorrhage.

We may call attention here to pains in the bones, which are a frequent cause of complaint—in fact, often the only complaint. In these cases I have not infrequently found percussion of the tibia or of the sternum painful. It is, therefore, possible that the pain in the limbs complained of by patients is attributable, at least in part, to the change in the bone-marrow which has been found in malaria. This pain on percussion is by no means constant.

In relation to the remainder of the lymphatic apparatus, we refer the reader to the Special Part.

CHLORANEMIA AND MELANEMIA.

The blood of the malaria patient always shows at some time the signs of an anemia or of a chloranemia—that is, of a chlorosis with an anemia. The discovery of the parasites demonstrated the reason for this anemia in the destruction of the red blood-corpuscles. That some of the blood-corpuscles succumb to a soluble parasitic toxin seems to me likewise probable.

In addition, there is frequently a decrease in the color coëfficient of the erythrocytes—in other words, a chlorosis. This is probably due to the fact that the bone-marrow, as a result of overproduction, sends into the circulation blood-corpuscles deficient in hemoglobin. This deficiency is gradually made up with an eventual return to normal; though in chronic malaria with subsequent cachexia the chloranemia may continue indefinitely.

It has been demonstrated by Kelsch that the greatest destruction of erythrocytes occurs during the first paroxysms, and that after a certain degree of anemia has been reached, this becomes gradually less.

The degree of anemia may be quite marked. Kelsch saw in one case 500,000 erythrocytes to the cubic millimeter*; in another case he observed within four days a reduction of erythrocytes to 2,000,000.

Dionisi saw, after individual pernicious paroxysms, losses of from 500,000 to 1,000,000 red blood-corpuscles.

My counts show the same; for instance, in a man with pernicious tertian: On the fourth day of the disease, erythrocytes, 3,131,250; hemoglobin, 60 per cent. One paroxysm. On the seventh day of the disease, erythrocytes, 2,112,500; hemoglobin, 45 per cent.; color index, about 1.1.

In a case of genuine quotidian: On the fourth day of the disease, erythrocytes, 4,978,000; hemoglobin, 100 per cent.

Two paroxysms. On the sixth day of the disease, erythrocytes, 4,012,000; hemoglobin, 85 per cent. No paroxysm. On the eighth day of the disease, erythrocytes, 3,110,000; hemoglobin, 60 per cent.; color index, over 0.9.

Here we see at the beginning of the disease, contrary to Kelsch's rule, no diminution (probably on account of the small number of parasites), yet later, in spite of the cessation of the paroxysms, new losses which were possibly the result of the deleterious effect of the malarial toxin not yet fully excreted.

In a case of quotidian of longer duration: Erythrocytes, 2,544,000; hemoglobin, 65 per cent. No paroxysm. Three days later, erythrocytes, 3,711,000; hemoglobin, 45 per cent.; color index, about 0.67. Here, therefore, there was a chloranemia.

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* The following figures, as is evident, relate to the number of erythrocytes in a cubic millimeter. My blood corpuscular counts were done with a Thoma-Zeiss apparatus; the estimation of the hemoglobin, with von Fleischl's hemometer.

In a case with irregular fever: In the third week of the disease, erythrocytes, 2,717,000; hemoglobin, 65 per cent. No paroxysm. Five days after the first examination, erythrocytes, 3,191,000; hemoglobin, 55 per cent.; color index, over 0.9.

In a case of typical tertian: In the third week of the disease, erythrocytes, 2,476,000; hemoglobin, 55 per cent. No paroxysm. Three days later, erythrocytes, 2,650,000; hemoglobin, 40 per cent.; color index, 0.8.

In the last three cases we find that, after the cessation of the fever, in spite of the increase in erythrocytes, the hemoglobin continued to diminish; in other cases the restoration of both went hand in hand.

Among the other appearances in the blood we must mention the great dissimilarity of the erythrocytes observed by Kelsch. In addition to normal sized corpuscles, Kelsch found abnormally large and small forms. Nucleated red blood-corpuscles have likewise been observed.

The leukocytes manifest no typical increase or diminution in malaria. In acute cases some leukopenia is usual. This transitory impoverishment of the circulating blood in leukocytes may be due to the accumulation of melaniferous leukocytes in the spleen. According to Vincent, a rapidly evanescent leukocytosis, only evident immediately after the beginning of the paroxysm, precedes the leukopenia. [This has been confirmed by Billet, who has shown that in regular charts of a tertian or quartan type the leukocytic curve bears a close relation to the temperature-curve.—Ed.]

Leukocytosis in the course of acute malaria points usually to complications (pneumonia, suppuration, etc.). Leukocytosis (according to Bastianelli, lymphocytosis) appears to be the rule only during paroxysms of blackwater and pernicious fever. In chronic infections it is not uncommon.

[With regard to the *relative* leukocytic count, many observations show that in malaria there is a marked increase in the percentage of large mononuclear leukocytes present, and this is often so marked, especially during periods of apyrexia, that it is possible, almost solely from this change, to diagnose a malarial infection in cases where parasites are absent, as after quinin or in blackwater fever. An increase to 20 per cent. of large mononuclear leukocytes is so suspicious that prolonged search will not uncommonly reveal a single parasite or so, or, if these be not found, pigmented leukocytes will almost certainly be found. As examples of this change we may quote the following:

(1)	Small mononuclear	18.1	per cent.	
	Large mononuclear and transitional	31.4	"	
	Polynuclear	50.2	"	
	Eosinophile	0.4	"	—(*Bastianelli.*)
(2)	Small mononuclear	19.1	per cent.	
	Large mononuclear and transitional	41.0	"	
	Polynuclear	39.0	"	
	Eosinophile	0.6	"	—(*Bastianelli.*)
(3)	Small mononuclear	18.1	per cent.	
	Large mononuclear and transitional	26.4	"	
	Polynuclear	55.3	"	—(*Panse.*)
(4)	Small mononuclear	14.8	per cent.	
	Large mononuclear and transitional	46.7	"	
	Polynuclear	38.5	"	—(*Stephens and Christophers.*)—Ed.]

Melanemia—that is, the occurrence of melanin in the blood—is a condition peculiar to malaria that may be demonstrated in every case, even though only at times. It constitutes, therefore, one of the fundamental characteristics of the disease, and possesses not only a theoretic, but also a practical, importance.

The origin of melanin has, since Laveran's discovery, been eventually explained. As previously stated, it is the product of digestion of the hemoglobin, and is elaborated in the body of the parasite. After destruction of the plasmodium (either by death or multiplication) this pigment is set free, is taken up as lifeless foreign matter by the circulating leukocytes, and is deposited in the different organs.

The dark color of certain organs (as the liver, spleen, brain) was recognized by the older investigators—for instance, Lancisi, Folchi, Bailly, Annesley, and others. The discovery of the pigment, microscopically, not alone in the organs, but also in the blood, was the work of Heinrich Meckel (1847); he found it in the body of an insane patient, and described in a classic way the "pigment cells" in the blood which were really the malarial parasites. The relation of this pigment to malaria was not remarked by Meckel, since he did not realize that the insane patient who had lived a long time in the asylum, and whose fatal disease had probably not been carefully studied, had died of pernicious malaria. This relation was soon after discovered by Virchow.

Almost simultaneously with Meckel, Dlauhy in Prague and Heschl in Vienna called attention to the malarial pigment. Virchow laid the site of origin in the spleen, whence it escaped into the blood. Other writers adopted his conclusions—for instance, Frerichs, who claimed the liver to be a second place of origin.

Planer hinted at the possibility of its origin in the circulating blood. Planer also seems to have been the first to observe the "pigment cells" in the living blood. Arnstein found that when death took place a long time after a paroxysm there was no melanemia, even though there might be pigmentation of the spleen, liver, and bone-marrow, and that melanemia was observed only when the death occurred a short time—at most forty-eight hours—after a paroxysm. He insisted, therefore, that the pigment was formed in the circulating blood, and supported his assertion with the observation that the distribution of the malarial pigment in the spleen, bone-marrow, and lymph-glands was exactly analogous to the distribution of pigment-granules introduced experimentally. These organs were consequently to be regarded, even in malaria, as places of deposit for those granules produced in the blood. Kelsch adopted a similar view, supported by the fact that there were cases of intense melanemia without a trace of pigment in the spleen. Kelsch assumed that in malaria a solution of hemoglobin in the blood plasma took place, which was later transformed into melanin.

C. Schwalbe, who witnessed melanosis in animals poisoned by carbon bisulphid and sulphur oxychlorid, referred the malaria to a similar poisoning, while Afanassiew looked on the pigment-granules as chromogenic cocci. Marchiafava eventually determined (1879) that the pigment was formed within the red blood-corpuscles.

With Laveran's discovery all these doubts were settled, yet we can only wonder at the acuteness of the earlier observers, some of whom came so near the truth. Virchow's view in regard to the origin of the pigment in the spleen was not so far wrong, since there are certain malarial infections in which the later stages of parasitic development take place, not in the circulating blood, but in the internal organs, particularly the spleen and bone-marrow.

Melanemia may be found at almost any time during a malarial infection—that is, as long as the malarial parasites continue to develop and increase. The most suitable time is shortly after or during a paroxysm, when the pigment is in the largest clumps and is, therefore, most readily recognized.

Moreover, the melanemia may continue after the disease has apparently passed and no paroxysms have occurred for some days. These are cases in which crescents continue the infection without producing manifestations.

At the termination of an infection the melanin disappears from the blood in a very short time, and forty-eight hours after the last paroxysm the most painstaking search usually fails to reveal it. This fact is very important, since it gives us a criterion for determining the cessation of the disease.

A positive melanemia practically assures the diagnosis of malaria. Apart from this disease, melanemia has been observed only in recurrent fever, in melanotic neoplasms, and in Addison's disease—in the first, only after a fever paroxysm; and in melanosarcoma (Nepveu) and Addison's disease, only very exceptionally.

I have frequently examined the blood of two cases of Addison's disease without finding any pigment. As regards the first two conditions I have had no personal experience.*

SKIN.

Changes are frequently found in the skin, yet since they are neither constant nor specific to this disease, they possess less of a diagnostic than of a general pathologic interest.

We have already described in another section the vasomotor disturbances manifested during the different stages of the paroxysm. We may mention further that an evident hyperalgesia of the skin is not uncommon during a paroxysm. I have observed it frequently on pricking the finger or the lobe of the ear for the purpose of examining the blood.

The exanthemata are more important. During an acute infection, herpes is frequent. This usually occurs on the nose, the lips, or the cheeks, although sometimes, too, on other places. Laveran mentions a case of herpes of the soft palate; I saw once a herpes of the left hand. Kelsch and Kiener maintain that it accompanied one-third of the cases of "bilious gastric" malaria. They observed it even on the hairy scalp. Yet F. Plehn saw, among 714 cases of West African fever, only one case of herpes.

In about the same frequency as herpes, urticaria is observed. This occurs sometimes with the paroxysms, sometimes independently of them. According to Kelsch and Kiener's experience, it seems to occur especially in grave cases. Erythema is less frequent, and appears in spots or may be distributed over the whole body. In children a peculiar form of erythema nodosum sometimes occurs (Obedénaire, Boïcesco, and Moncorvo). This is manifested by quite prominent, painful nodes situated on the arms and legs. They are dark red in color, especially during the paroxysms, and pass away without suppuration. Such an erythema can be regarded as only part of the disease-picture, when no drugs have been previously administered which might produce such a condition (quinin, antipyrin, etc.).

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* Latschenberger observed pigment-granules in the circulating blood of guinea-pigs and frogs, as well as other species of animals, the blood of which contains hemoglobin I cannot say whether or not these occur physiologically in human blood, yet there is no reason for confusing them with melanin, if my rule is followed to consider as positive only the pigment found in leukocytes.

Roseola is a very rare symptom of malaria, and one I have personally never observed. Purpura has been seen in rare cases. The opinion of some writers that herpes zoster is connected with malaria seems to me unfounded (Winfield affirms that he found malarial parasites in 8 cases of zoster [?]).

After the disease has continued a long time the skin becomes strikingly pale, and takes on an ashen-gray to light yellow color. This is the well-known color of the malarial cachectic. The discoloration is always diffuse, even though here and there the skin may be somewhat speckled as a result of the unequal distribution of the pigment. The mucous membrane assumes also a diffuse grayish or light yellowish color, without showing the pigmentation peculiar to Addison's disease.

A more evident yellowish color—in other words, icterus—is not rare. When it occurs, it is usually slight, though it may be marked. This icterus of acute malaria is the so-called "urobilin icterus," since the urine contains only urobilin and not bilirubin.

Edema of the lower extremities sometimes occurs after malarial infections, or even during them, when the patient does not take to bed.

Anthrax, erysipelas, phlegmon, and noma sometimes complicate the severe forms, and are naturally to be regarded as secondary infections. Gangrene of varying extent and distribution is not rarely observed after severe infections.

URINE.

The peculiarities presented by the urine differ somewhat from those which we are accustomed to find in other infectious diseases, yet they are not sufficiently definite to be considered characteristic.

As to the amount, the great majority of cases manifest a not inconsiderable polyuria, and this increased excretion is usually observed on days when paroxysms take place. Two to four liters are not rare. This is the more striking on account of the organism losing so large an amount of water by the profuse sweating. A postmalarial polyuria is even more frequent, and it may develop to such a degree as to be appropriately designated a postmalarial diabetes insipidus.

This postmalarial diabetes was recognized by Sydenham. It was recently studied by Mossé. Among 100 cases of malaria, he found an increase in the amount of urine 11 times. The polyuria began three to six days after the last paroxysm, quickly increased to its acme, then rapidly diminished, although it continued in a lessened degree for a long time. The patients usually left the hospital still showing it. The largest daily amount observed by Mossé was eight liters. The daily excretion of urea during the polyuria was normal, but the chlorids were considerably increased, usually about double. In one case 65 gm. were excreted within twenty-four hours.

Some observers affirm that during the cold stage the urine is light in color and profuse; during the hot stage, scanty, and during the sweating stage, highly concentrated and especially large in amount. This may be true for some cases, but it is by no means constant. The old physicians laid great diagnostic value, especially in latent cases, on the lateritious sediment.

The specific gravity varies, and in pronounced polyuria is not always correspondingly low. As was first demonstrated by Traube and Jochmann, the percentage of urea and chlorids increases with the paroxysm and falls after it. Sydney Ringer, Hirtz, and Jaccoud found that the increased excretion of urea began several hours before the paroxysm, reached its acme toward the end of the cold stage, and then fell, though it continued over the normal.

According to Ringer, the increase in urea is in proportion to the rise of temperature. Redtenbacher found in ten cases the amount of urea and urine increased (even to three and one-fifth times the normal) during the paroxysm, and diminished during the apyrexia. Uric acid appears to show no noticeable deviations from the normal.

Rem-picci, Caccini, and Bernasconi recently found, among 37 cases, the chlorids increased in 22, normal in 6, diminished in 9. The amount of chlorids was proportional to the amount of urine. The chlorids were found diminished by Hammond and Uhle. According to Gee, Rosenstein, and others, the phosphates are decreased during the paroxysms and increased during the defervescence. Rem-picci, Caccini, and Bernasconi found the phosphates diminished during the entire paroxysm and increased during the apyrexia.

The amount of iron in the urine was found increased by Colasanti and Jacoangeli.

Among the abnormal constituents, serum-albumin is not uncommon. It is found during the paroxysm in larger or smaller amounts. Martin Solon reported its presence in one-fourth of the severe cases, Osler 133 times in 333 cases, Marchoux 39 times in 40 cases. The albuminuria disappears in the majority of cases with the cessation of the paroxysms, yet there are not a few cases in which the albuminuria continued two to three weeks or ever longer. (For further details see section on Complications and Sequelæ.)

I have repeatedly found nucleo-albumin in traces or more evident amounts during or shortly after the paroxysm. Peptone was found regularly during the paroxysm and for a few days after by Dubujadoux.

Acetone and diacetic acid have been occasionally observed in severe cases during the paroxysm.

Glycosuria has been frequently reported. Burdel speaks of it as a common symptom. The largest amount of sugar which he met with was 12 per cent. In 60 cases Range found in no instance a marked reduction of the copper solution; a slight reduction in 24. In 72 cases Sorel observed a fleeting excretion of small amounts of sugar in only a few. Mossé saw transitory glycosuria twice in 100 cases, and even these two are not above suspicion, since one was a midwife, the other a patient suffering simultaneously from arthritis. Laveran, Kelsch and Kiener, and others were also unable to confirm Burdel's assertion. In my cases I found only one: a ten-year-old girl with double tertian, whose urine, passed during the paroxysm, showed nucleo-albumin, albumin, considerable acetone, and a marked reducing substance. The urine responded also to the phenylhydrazin test, but showed no rotatory power in the polariscope; the reducing substance was, therefore, not sugar. It appeared again with every paroxysm.

Bilirubin is rarely observed, while urobilin is almost constant and often in considerable quantities. Indican is frequently increased. Ehrlich's diazo-reaction responds in a few cases. (For hemoglobinuria see the section devoted to it.)

Microscopically we often find in the albuminous urine of the paroxysm isolated hyaline or granular casts, red and white blood-corpuscles, and kidney epithelium.

According to the experimental investigations of Roque and Lemoine, the urine passed after a paroxysm possesses markedly toxic properties. They found, for instance, that the hypertoxic coëfficient before a severe paroxysm = 0.130; after it, 0.684; and once, 0.752. Following the administration of quinin, the coëfficient increased for twelve hours to 1.276 and then fell.

NERVOUS SYSTEM.

The malarial virus possesses a particular affinity for the nervous system, and to this is attributable many of the symptoms that characterize the clinical picture. It is well known that before the recognition of the true cause malaria was often regarded as a "neurosis" (van Swieten). This hypothesis was the predominating one until shortly before Laveran's discovery, and though absolutely without foundation, there is a grain of truth connected with it. There is no doubt, for instance, that that most characteristic symptom of malaria —the classic paroxysm—is due to an effect on the nervous system. The difference between the theory of to-day and formerly is only this: Formerly the paroxysm was regarded as an expression of diseased vasomotor nerve-centers, while we now realize that the disease virus circulates in the blood and the paroxysm is the reaction of the nervous system to the intoxication. It might be said that the vasomotor centers sound the alarm signals announcing the entrance of the enemy. In this metamorphosed condition the nervous factor of the old hypothesis has been preserved.

It is of general pathologic interest to notice cases in which a disturbance of the nerve tracts already exists. In these the regions to which the tracts are interrupted do not participate in the paroxysm. I once saw a case of right-sided paralysis of the extremities as a result of a lesion of the pons. The man became affected with malaria and claimed that during the chill only the left half of the body shook.

Knapp observed a case suffering from complete sensory and motor paraplegia as a result of a fracture of the tenth dorsal vertebra. During a paroxysm the paralyzed portions were not affected, while the upper portion of the body manifested all the symptoms (quoted from Griesinger).

But it is not alone the vasomotor centers that react to the malarial toxin: a whole series of nervous symptoms, of varying intensity, show us that all the other parts of the nervous system likewise participate. There is scarcely a nervous symptom known that has not occasionally been observed in malaria.

The sensorium shows every alteration from the lightest stupor to the deepest coma, from psychic depression to insanity. Headache in a light or severe form accompanies almost every paroxysm. Neuralgia is frequent, and occurs especially in the first and second branches of the fifth nerve, though also in other nerves, like the sciatic and intercostal, and the celiac plexus. Symmetric gangrene demonstrates the participation of the trophic nerves. Aphasia, hemiplegia, paraplegia, irritative motor symptoms in the shape of epileptiform and tetanoid convulsions, reflex convulsions, singultus, sneezing, yawning, vomiting, coughing, and secretion neuroses like polyuria, hyperidrosis, etc., have been observed.

Naturally it is not always easy to determine how much of these manifestations is to be laid to the door of the poison, how much to other effects, like the occlusion of vessels. Yet omitting everything doubtful, we have still a sufficient number of assured observations to prove that the toxin of the malarial parasite is, in the first place, a nerve poison.

The nervous symptoms are especially conspicuous in infections with the pernicious parasites, and they sometimes so dominate the clinical picture that special names have been applied to the syndromes which they produce. But we will take this up in the special part.

GASTRO-INTESTINAL TRACT, RESPIRATORY TRACT, CIRCULATORY APPARATUS.

The gastro-intestinal tract frequently participates in the malarial infection. Loss of appetite, eructation, a feeling of weight in the stomach, vomiting, cardialgia, are very common symptoms at the beginning of the paroxysm. True, it cannot be determined in every case which symptoms are to be attributed to nervous disturbances and which to direct participation of the stomach, since the two factors often act together. On the part of the intestine, diarrhea is the most frequent occurrence. This is sometimes so severe as to suggest cholera or dysentery.

Icterus, or at least a subicteric discoloration, depending on whether the icterus is due to a gastroduodenal catarrh or polycholia, is not uncommon.

The respiratory tract participates frequently in the form of a catarrh affecting usually the bronchi. A dry cough is not rarely observed during the paroxysms, and objectively we may find here and there a few râles. Moreover, during the cold stage dyspnea may occur, though rarely orthopnea.

The circulatory apparatus is affected least of all, and only indirectly. The narrowing of the arterioles during the cold stage leads to an increase of blood-pressure; the subsequent dilatation during the hot stage, to a decrease. Corresponding to this, the pulse in the first stage is small and tense; in the second and third, full, soft, and exquisitely dicrotic (Figs. 13–17).

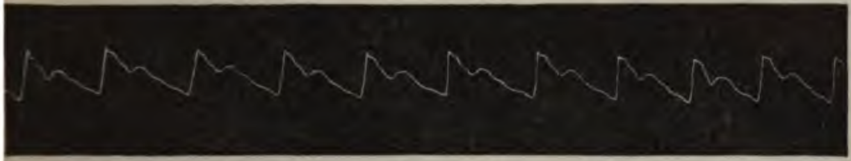

FIG. 13.—PULSE-CURVE OF A DOUBLE TERTIAN DURING APYREXIA. Temperature, 36.5° C. (97.7° F.); pulse, 54; respiration, 14.

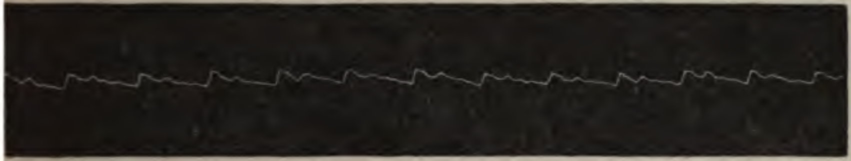

FIG. 14.—THE SAME CASE AT THE BEGINNING OF THE COLD STAGE. Temperature, 38.2° C. (100.7° F.); pulse, 104.

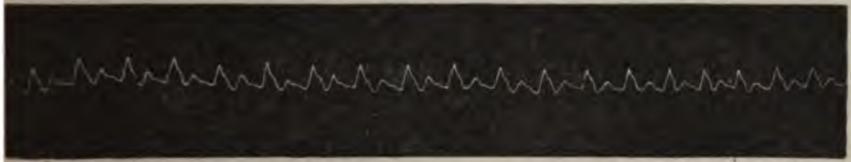

FIG. 15.—THE SAME CASE DURING THE COLD STAGE. Temperature, 40.2° C. (104.4° F.); pulse, 134; respiration, 20.

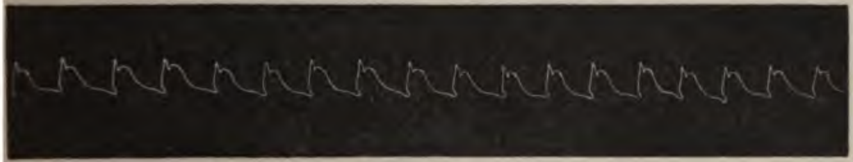

FIG. 16.—THE SAME CASE AT THE BEGINNING OF THE HOT STAGE. Temperature, 38.7° C. (101.6° F.); pulse, 92.

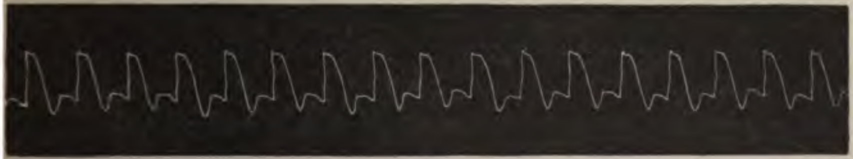

FIG. 17.—MALIGNANT TERTIAN DURING HOT STAGE. Temperature, 39.2° C. (102.6° F.) (anadicrotism).

The pulse usually increases in frequency with the rise of temperature, so that during the acme of a paroxysm we often find it

120 to 140. Sometimes it is less than the temperature would call for. During the apyrexia the pulse promptly falls in frequency, sometimes even to slight brachycardia. A slight degree of arhythmia at the beginning or end of the paroxysm occasionally occurs, yet seldom becomes a prominent symptom.

The increase of blood-pressure during the cold stage may lead to rupture of vessels, especially in the brain. Sebastian reports the rupture of the right auricle of the heart during this stage. Duroziez and Lancereaux report endocarditis in causal connection with malaria. Laveran denies that malaria can produce either endocarditis or pericarditis, and assumes in these two cases a coincidental association. From my own experience I would take Laveran's view. In relation to this further details are given in the Special Part.

SPECIAL PART.

CLASSIFICATION OF MALARIAL DISEASES.

In the classification of malarial diseases our purpose is to separate the actual disease from its sequelæ. Our considerations, therefore, will concern the fully developed infection.

All who have attempted such a classification have found the way paved with difficulties, and but few have been able to combine the necessary conciseness with completeness. Until very recently the type of fever and the clinical symptoms were employed as the base of classification, and depending on whether one or the other factor was regarded as the more important, the scheme of classification differed.

Laveran's discovery of the parasites and Golgi's demonstration of the different species have laid for us a foundation for a rational classification. Yet such a division is possible only if definite clinical symptoms correspond to the different species of parasites. In our experience this clinical requirement is present and we can, therefore, abandon the old classifications and replace them by one constructed on a parasitologic basis. Moreover, we will see that even while adhering to this etiologic point of view; the clinical syndrome will not be neglected; on the contrary, the clinical symptoms will be allowed to influence the division of details.

Corresponding to the parasites, we divide malarial fevers into two principal groups:

I. Fevers produced by Golgi's common tertian and quartan parasites.

II. Fevers produced by crescent-forming parasites. To which we add:

III. Fevers produced by an association of both species of parasites (mixed infections).

IV. Latent fevers.*

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* It is evident that in preserving the group "latent fevers" we have deviated from the pure etiologic classification in order to meet the clinical requirements. Blood-examinations of latent fevers are as yet too few to make it possible to omit this group by combining it with the others.

1. FEVERS CAUSED BY GOLGI'S COMMON TERTIAN AND QUARTAN PARASITES.

General Characteristics.—The fevers in this group are characterized by definite peculiarities by which they may be classified under one clinical head.

These fevers are relatively less frequent to tropical and subtropical regions than to temperate climes, where they usually occur alone. In tropical and subtropical countries they appear in their pure form only in the cooler half of the year, especially at the beginning of spring; while in the temperate climates they occur as primary infections even in summer and autumn.

They are characterized clinically by paroxysms, which adhere to a pretty definite type: in other words, they belong among the typical intermittent fevers. At the beginning of the disease a remittent or continued fever may occur, from which the typical paroxysms eventually develop, though this is only exceptional. The paroxysms a e usually well developed and show three stages that are readily differentiated. These fevers extremely rarely manifest a pernicious character, and are almost never fatal unless as a result of complications.* At the acme of the paroxysm, suggestions of serious symptoms may arise, but they quickly disappear.

The treatment of these fevers is very satisfactory. Quinin acts promptly, as a rule, in twenty-four to forty-eight hours. Relapses occur, but are much less frequent than in fevers of the second group, and usually appear to be due to insufficient therapy or new infection. As a result of the characteristic symptoms of this infection the clinical picture presented by it is quite monotonous. The different organs participate in a regularly mild way and no local phenomena are to be anticipated. Moreover, the diagnosis is usually very easy, and is, as a rule, recognized by the patient or his friends.

Corresponding to the species of parasites that come into consideration these fevers divide themselves into: 1. Quartan fever. 2. Tertian fever. 3. Mixed fever.

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* Although Torti, in his communication to Mercatus (*loc. cit.*, Lib. ii, Cap. ii, Scholium 1), affirms that not only the tertian, but even the quartan, may become pernicious, this is only an apparent contradiction of the standpoint which we have taken. When Torti spoke of the quartan becoming pernicious, he meant that it might become so, after being transformed into a continued. This is evident from the following (Torti, Lib. iii, Cap. i): "Primo necat hominem perniciosa intermittens potissimum tertiana (quartana etenim, aliave intermittens rariuscule in primo membro nostræ divisionis locum habere solet, sæpius vero in secundo, ubi ad continuitatem vergat et ad acquirendam acutiem). . . . ."

QUARTAN FEVER, THAT IS, FEVER CAUSED BY THE QUARTAN PARASITES.

It is a general, well-confirmed fact that quartan is the least frequent of all malarial fevers. There are malarial districts where it does not occur at all. The following figures will best illustrate this:

Maillot counted in Bona (Algeria)....	among	2338	malarial	cases,	26	quartan	fevers.
Finot in Blida	"	4211	"	"	21	"	"
Durand de Lunnel in Ténès..........	"	625	"	"	6	"	"
Osler in Baltimore	"	616	"	"	5	"	"
Laveran in Algiers	"	311	"	"	7	"	"
Griesinger in Tübingen	"	414	"	"	3	"	"

Among my 144 malarial cases there were 4 assured cases of quartan. A further 4 cases were, according to the blood examination, likewise quartan, but since they were treated in the ambulatory, their fever-curve is unknown. Not one of these eight cases was acquired in Vienna. I may say, therefore, that in Vienna at the present time quartan fever does not arise autochthonously.

Crombie affirms that during a twenty-two years' experience in India he observed but one case of quartan. [The recent researches of Stephens and Christophers have shown that in certain districts of India among the natives, quartan alone prevails, and it must now be considered to be common in India.—Ed.]

There are, so it seems, only a few places where quartan predominates. Trousseau stated that in Saumur quartan, in Tours only tertian, occurred. According to Calundruccio, in Gebbia Liberto near Fiumefreddo (Sicily) only quartan is seen. According to all authorities in Seul, quartan and tertian are equally common; in the southern provinces of Corea quartan is much more frequent than tertian.

The assertions of many older writers and some recent ones that quartan appears only after repeated relapses is, from my observations, incorrect. Quartan fever occurs as a primary infection, just as tertian or quotidian.

The type of the simple quartan fever—that is, the fever caused by one single generation of quartan parasites—may be represented in the following way: $\overbrace{100}\overbrace{1001}$, etc. Between two paroxysmal days, therefore, there occur two days free from paroxysms.

A second type of quartan fever arises as a result of the presence of two generations of quartan parasites. These commonly show a difference in age of twenty-four hours. This is represented, therefore: $\rlap{\overbrace{}\overbrace{}}1\underbrace{101}\underbrace{101}1$. This type is characterized by two paroxysmal days following each other, and then a day free from paroxysms.

This type is very rare, and there are experienced investigators (for instance, Griesinger) who have never observed it and consider its occurrence questionable.* I have had the good fortune to observe two such cases, the typical curves of which left no doubt as to their significance (Figs. 19 and 20).

A third type occurs when three generations with a 24-hour age interval circulate in the blood: $\rlap{\overbrace{}\overbrace{}\overbrace{}}\rlap{1\underbrace{}\underbrace{}}11\underbrace{111\vphantom{\underbrace{1}}}\underbrace{111\vphantom{\underbrace{1}}}11$. It is, therefore, clinically a quotidian type.

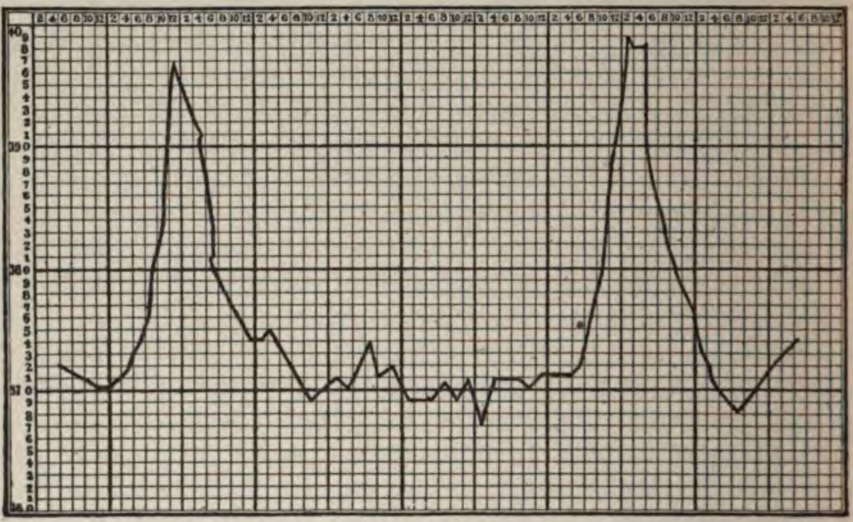

FIG. 18.—SIMPLE QUARTAN (after Silvestrini).

In quartan fever the paroxysm is usually fully developed and the temperature often reaches considerable heights. The curve rises quickly and falls quickly, so that a point is made, yet a disturbance may occur, making a double summit (Fig. 20). This is explained on the assumption that the sporulation of a part of the parasites occurs somewhat earlier than that of the remainder.

The duration of the paroxysm is ordinarily six to twelve hours. Only rarely are the paroxysms so prolonged that the second appears

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* The plural quartan type was recognized even by the ancients. Celsus speaks of "Duæ quartanæ" and of "Febris quotidiana, quæ ex quartanæ facta est" (Lib. iii, Cap. xvi and xvii).

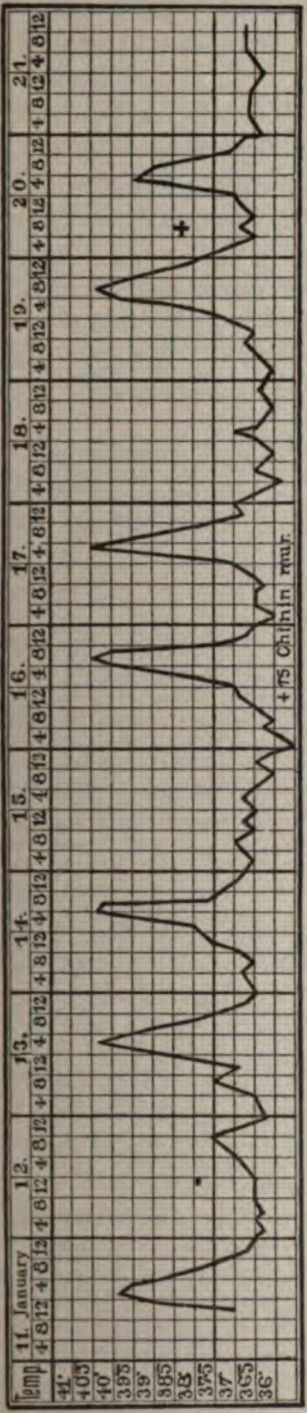

FIG. 19.—DOUBLE QUARTAN.

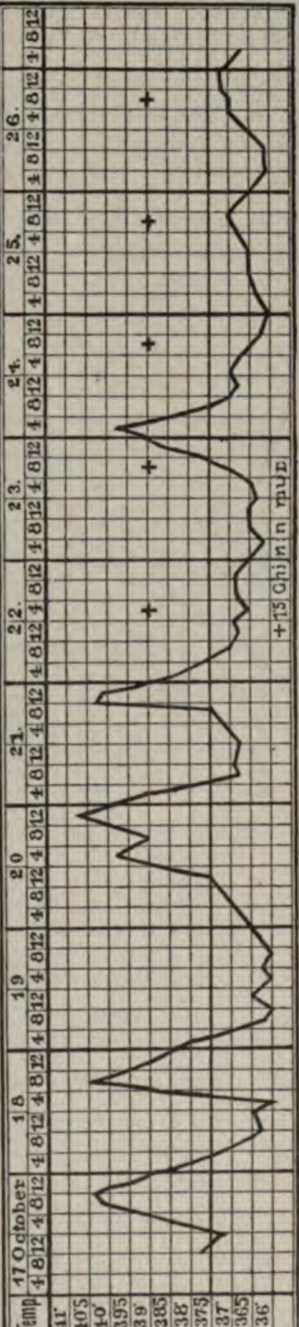

FIG. 20.—DOUBLE QUARTAN.

before the first has terminated, giving rise to a subintrant quartan. This occurrence is almost confined to plural quartan infection (especially triple quartan). It is a "benigna continuitas" (Torti).

A change of type in quartan fever is possible only in the ways described for the three types, and a transformation of quartan into tertian, or vice versâ, without the occurrence of a new infection, is impossible. The older writers, like Griesinger, and the more recent ones, like Hertz, follow only a hypothetic outline when they write that tertian may "go over into" quartan by postponement, and this by anticipation into tertian. I consider this as unlikely as that a typhoid fever should "go over into" a miliary tuberculosis. From among neither my own observations nor those of others have I ever been able to find anything that would justify such an idea.

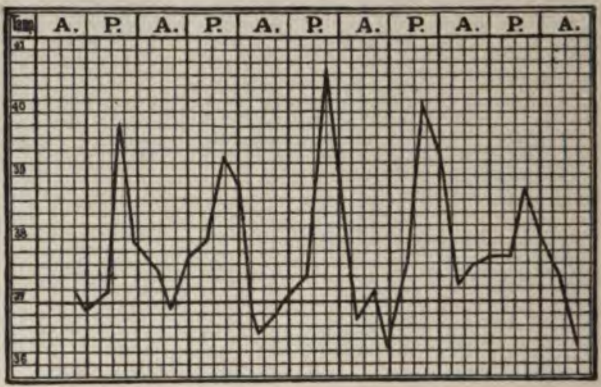

FIG. 21.—TRIPLE QUARTAN (from Marchiafava and Bignami).

The other associated symptoms of quartan fever remain within the limits prescribed in general to this group of fevers. On the part of the nervous system we frequently see headache, brightness of the eyes, somnolence, light twitchings in the region of the facial nerve, mild delirium, etc. Vomiting or diarrhea is frequently present, as is likewise dyspnea during the cold stage. Anemia occurs and develops the more rapidly the more numerous the generations of parasites and the greater the number of parasites in each generation.

Quartan has the reputation of particular obstinacy in regard to relapses. Unfortunately, there are no statistics on this point. I consider it possible that the long intervals predispose to a less energetic therapy than is necessary for the prevention of a relapse. In my experience, at least, the effect of quinin is as evident in quartan as in tertian. Only a large number of statistics could show if the old Roman saying, "Quartana te teneat," is or is not justified in the age of quinin. Yet from the experiences of the old writers it may be concluded that of all malarial infections, quartan shows the least inclination to spontaneous recovery. It appeared, therefore, to some observers as almost incurable.

TERTIAN FEVER—FEVER CAUSED BY THE COMMON TERTIAN PARASITES.

This is the most frequent fever of the temperate zone. Among my 143 cases, 88 were tertian; among 71 observed by me in Vienna, 61 were tertian; among 72 in Dalmatia and Croatia, 27 were tertian. From these statistics we can see to what an extent this form may predominate in mild malarial regions, and what a secondary place it may occupy in severe fever regions.*

The type of fever depends on whether one or two generations of parasites are present in the blood. In the first case, the type will correspond to $\overbrace{101010101}$; in the second, to $\overbrace{1\underbrace{1111111}1}$, or quotidian. In the second case we have, therefore, a double tertian. This doubling of the tertian fever is extremely frequent—much more frequent than the doubling of the quartan fever previously described. Among my 88 cases of tertian fever 43 were doubled; in other words, almost half the cases.

The existence of a double tertian may often be recognized from the fever-curve in that the paroxysms of the different series may differ in intensity or occur at different times in the day. As is well known, the ancient writers recognized and properly described this doubling. Much more rarely the doubling occurs in such a way that two paroxysms take place every third day. The anticipating type is frequent, the postponing less so. The latter arises usually as the result of therapy. In regard to the description of the paroxysms, what was said in relation to quartan may be repeated here.†

The curve in tertian usually rises uninterruptedly and falls again

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* Still I must mention that these figures require a correction, inasmuch as the Vienna cases were drawn from all seasons of the year, while the southern ones were limited to the months August and September—in other words, times at which the fevers of the second group are especially predominant.

† It was scarcely correct when Galen said: "Tertianam quidem a quartana qui, primo statim die, nescit distinguere, neque ommino medicus est." Though by means of the microscope, we are to-day in a position to justify Galen's requirements.

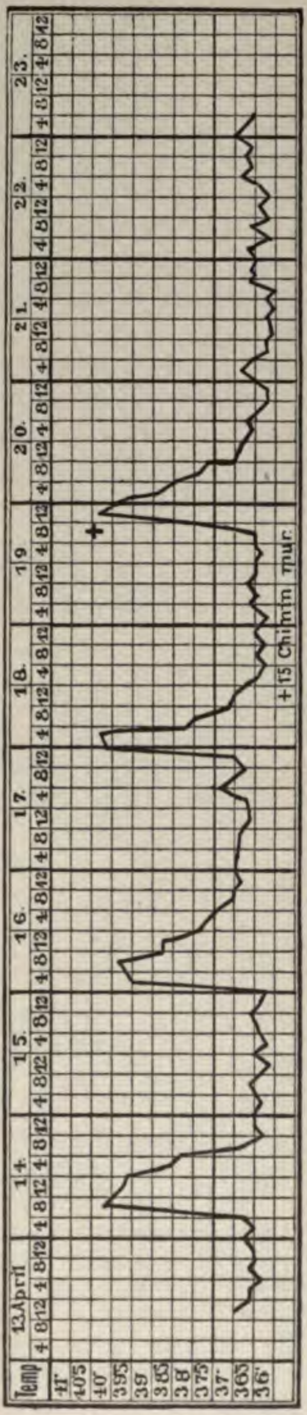

FIG. 22.—SIMPLE TERTIAN (ANTICIPATING).

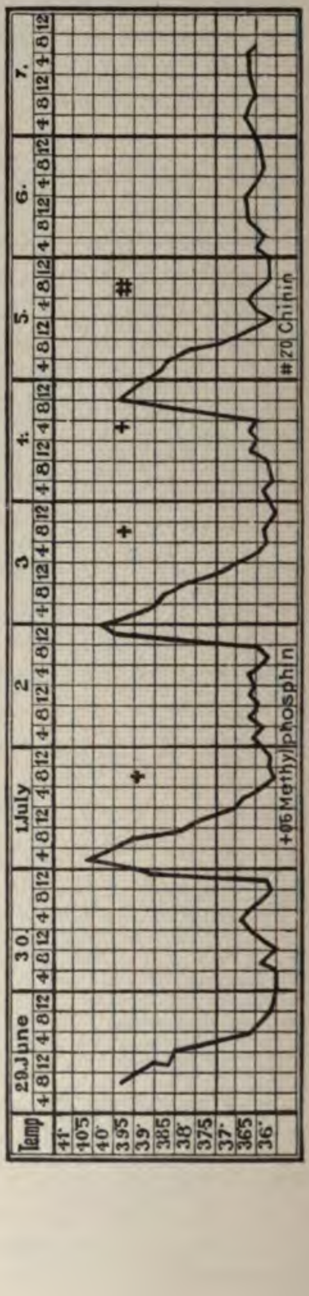

FIG. 23.—SIMPLE TERTIAN (ANTICIPATING).

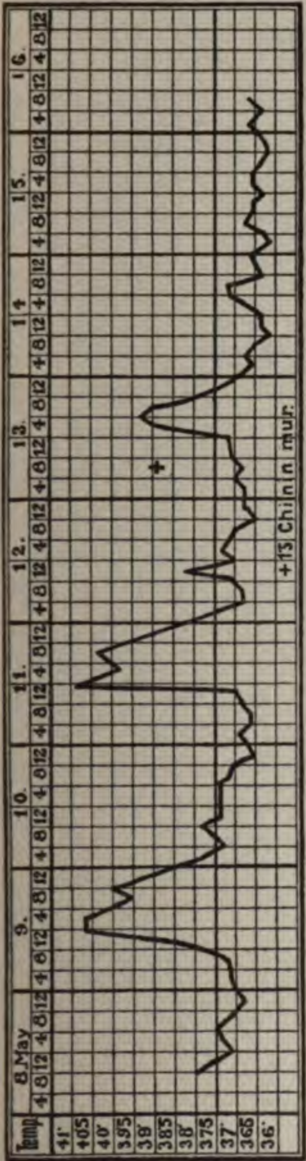

FIG. 24.—SIMPLE TERTIAN.

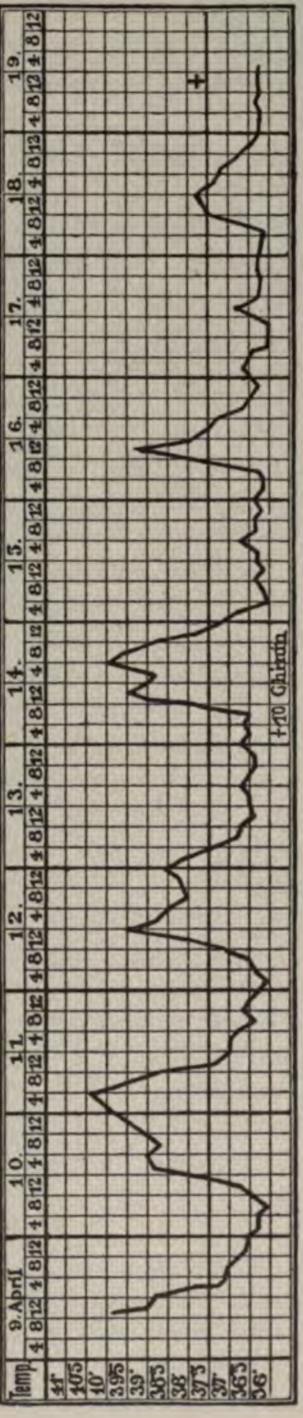

FIG. 25.—SIMPLE TERTIAN AND PROLONGED PAROXYSMS.

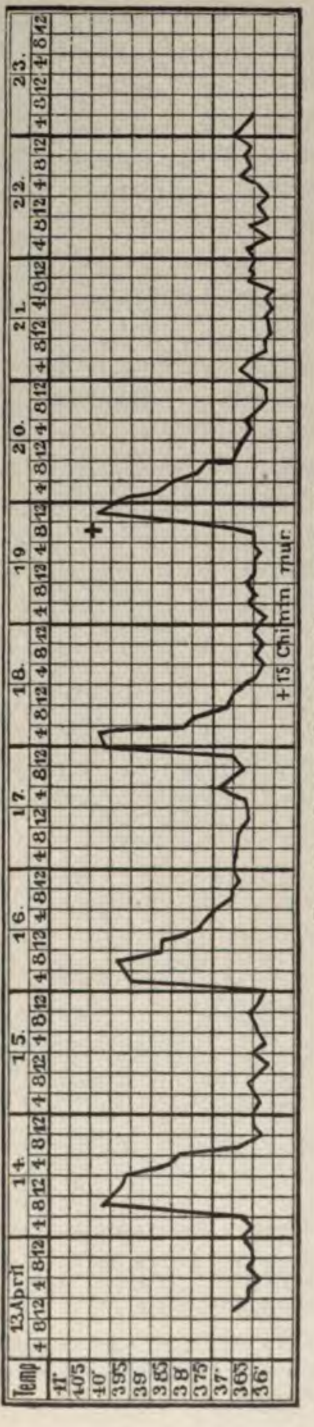

FIG. 22.—SIMPLE TERTIAN (ANTICIPATING).

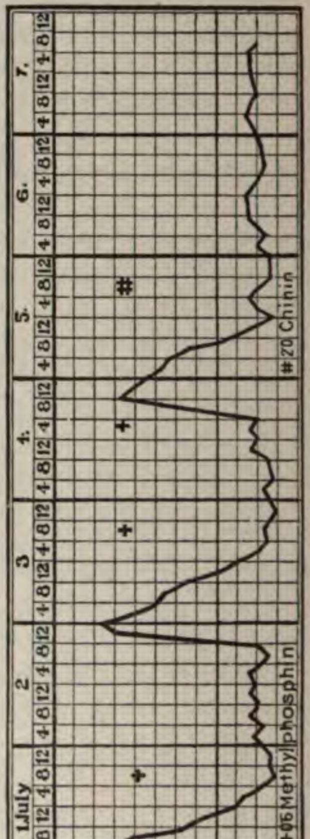

FIG. 23.—SIMPLE TERTIAN (ANTICIPATING).

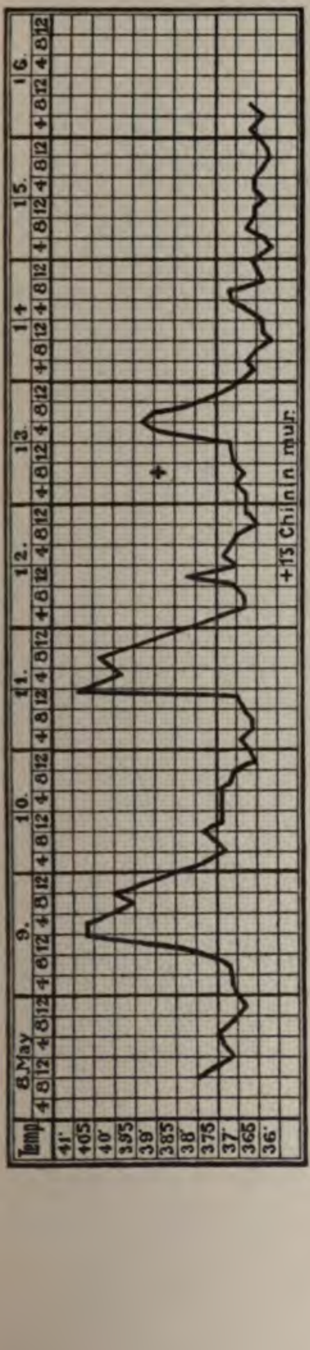

FIG. 24.—SIMPLE TERTIAN.

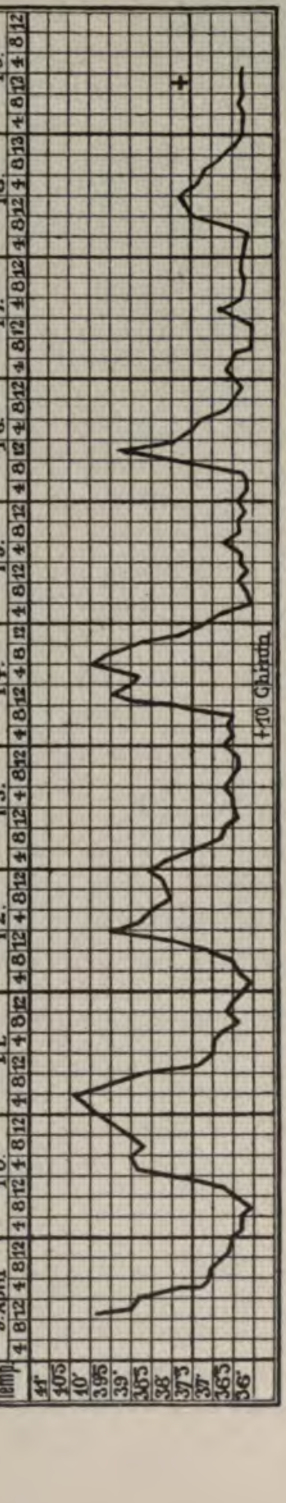

FIG. 25.—SIMPLE TERTIAN AND PROLONGED PAROXYSMS.

in the same manner. Yet it may happen that after a slight fall a new rise appears before the final decline takes place. In this way the duration of a paroxysm may be prolonged. This usually lasts from six or eight to twelve (rarely only four) hours, but by this complication it may be lengthened out to twenty-four or thirty-six hours and even more (Figs. 24 and 25). In these cases it occasionally happens that a chill occurs before the second rise, making twin paroxysms, caused by two very closely related generations of parasites.

By the prolongation of a paroxysm in double tertian it may happen that the beginning of a new paroxysm falls within the fever period of the preceding one; we then speak of subintrant benign tertian. If more than two generations of parasites are present,—in other words, if the paroxysms run together not on account of prolongation, but on account of the multiplication of different generations, though this is rare,—we have what we designate as subcontinued benign tertian. (See Fig. 28.)

Irregular febrile movements are sometimes observed, though not frequently; they occur especially at the beginning of the infection.

Change of type is common, though limited to the types just described. Quartan type, I repeat, does not alternate with tertian without a new infection. The change of type is seen most frequently in relapses, in that, for instance, during the primary disease, we see simple tertian, during the relapse,—whether this occurs after treatment with quinin or spontaneous recovery,—a double tertian type, or vice versâ. In other cases a gradually increasing curve developing on the days between the paroxysms announces the doubling. The reverse—the falling-out of a generation—is not infrequently seen in cases of incomplete treatment.

Recovery occurs promptly under quinin, and though the first paroxysm after its administration may not be completely prevented, it is usually modified and lessened in intensity. With proper treatment a second paroxysm is scarcely ever seen, yet when the quinin is not continued sufficiently long, relapses are frequent. These occur usually two or three weeks after the last paroxysm.

MIXED FEVERS.

Simultaneous infection with quartan and tertian parasites is, at least in our experience, a rare occurrence. It is evident that the resulting fever-curve would be no simple intermittent. On the contrary, we would see, according to the relative ages of the different generations of parasites and according to their numbers, marked

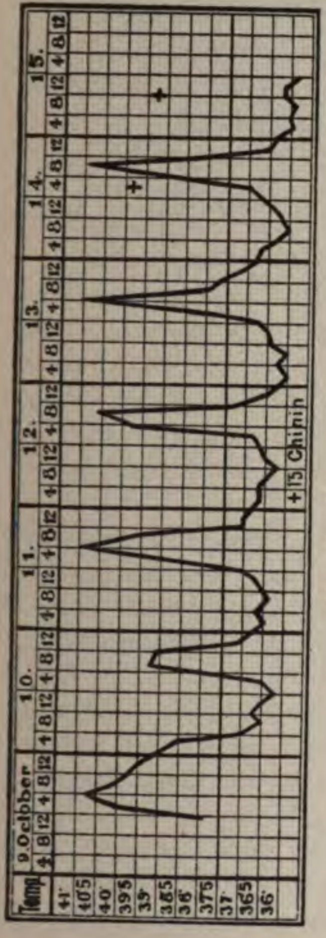

FIG. 26.—DOUBLE TERTIAN.

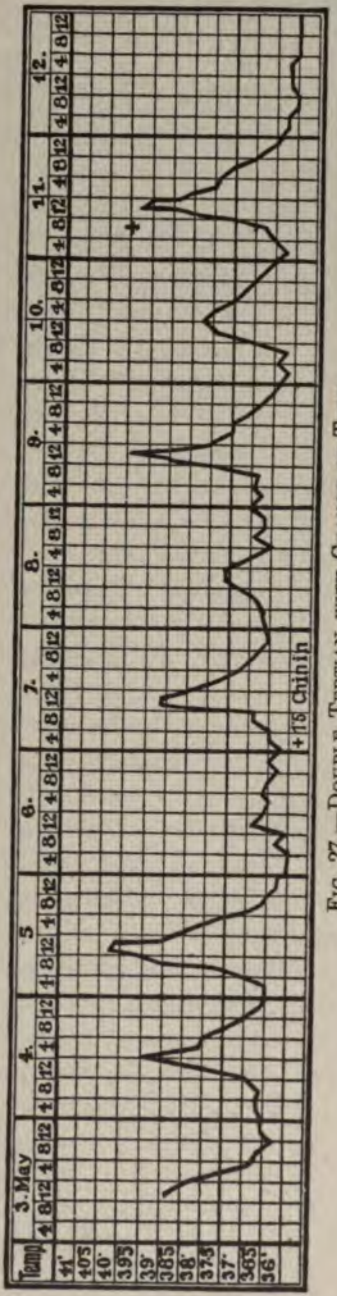

FIG. 27.—DOUBLE TERTIAN WITH CHANGE OF TYPE.

deviations in the shape of intermittent, alternating with continued or subintrant, fever.

FEVERS CAUSED BY CRESCENT-FORMING PARASITES.

General Characteristics.—The fevers belonging to this group are endemic in the severe malarial regions of the tropical and subtropical zone, and constitute there the predominant infection. Still there are not a few places in the temperate zone where they are endemic—for instance, the Roman Campagna, Sicily, Greece, Dalmatia, Croatia, etc. They occur here only at the height of summer and in autumn, and have been designated, therefore, by Italian writers, as "febbri estivo-autunnali" (summer-autumn fevers).

Moreover, they are not absolutely confined to the south. They have been repeatedly observed, even to an epidemic extent, in northern Europe. According to Hjelt, remittent fevers have been seen during isolated epidemics in Finland, up to latitude 61°. These occurred in August and were called August fever. They undoubtedly belong to this group. Similar fevers were observed in large numbers at the beginning of the seventy years' war in Wilhelmshaven. Isolated endemic foci are found in France, Holland, Hannover, and Holstein.

It is to these fevers that innumerable human lives have been sacrificed in tropical countries; it is these that present the greatest difficulties in the way of colonization by decimating the settlers. They have become, therefore, a great factor in national economy, with which the most powerful states have to reckon.

Having described the monotony of the clinical picture as the most striking peculiarity of the fevers under group I, we may say that the fevers of this group present a protean multiplicity of symptoms such as is seen in few infectious diseases.

Apart from the inevitable anemia, there is scarcely a second symptom which we can describe as of constant occurrence. The grouping of the various symptoms which may give rise to differential diagnostic difficulties with the most heterogeneous diseases—typhoid, cholera, yellow fever, psychoses, etc.—is more or less arbitrary.

The most important feature differentiating the fevers of this group from those of the first is their perniciousness. This does not insinuate that all the fevers caused by the small crescent-forming parasite are pernicious in the sense that they show, without exception, symptoms dangerous to life, but only that they may show, and not infrequently do show, such symptoms, while the fevers of the first group scarcely ever become pernicious, even in this sense. It is, therefore, evident that the microscope may reveal not only the diagnosis, but also the prognosis and the therapy.

Moreover, a certain malignancy is attached even to these cases, which run their course without pernicious symptoms, inasmuch as in spite of energetic treatment with quinin they obstinately relapse and frequently produce severe anemia, cachexia, and other sequelæ.

In a **classification** of these fevers it would be logical to divide them into two groups, corresponding to the parasites causing them, namely, quotidian and tertian. But this is not at the present time practical, since the characteristics of the parasites have not yet been sufficiently established to make them the basis of a rational diagnosis. Moreover, the multiple infections and mixed infections that occur so commonly, and the frequent differences in the periods of evolution of the parasites in different individuals, would make the matter so complicated that a division would be the cause of more confusion than elucidation. Finally, this division may be dispensed with, for the reason that the symptoms, both when caused by the quotidian parasites and the malignant tertian parasites, seem to be identical.

We will, therefore, avoid every fixed classification and endeavor to describe the complete symptom-complex of these fevers in a general or detailed way, as may seem necessary.

TYPE OF FEVER.

Corresponding to the parasites causing the fevers, the two types are quotidian and tertian; quartan does not occur.*

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* In regard to the relative frequency of the two types in different places, there are but few data. A decision as to whether a certain case is quotidian or tertian is often especially difficult, on account of the irregularity of the fever-curve. It appears to depend somewhat on the geographic location as to which of the two types predominates.

Burton Brown observed in Lahore 95 per cent. of quotidian, about 3 per cent. of tertian, and 2 per cent. of other kinds of fever. According to Marchiafava and Bignami, among the Roman estivo-autumnal fevers, tertian predominates.

Thayer and Hewetson observed in Baltimore, among 105 cases of estivo-autumnal, 38 with intermittent quotidian, 16 with quotidian, showing an inclination to continued, 13 with continued, showing quotidian exacerbations, 6 with tertian, the remainder with either no fever or an undetermined irregular one. Taken altogether, therefore, there were 67 quotidian as compared with 6 tertian.

Among 50 estivo-autumnal fevers I observed 18 quotidian, 14 tertian, and 18 irregular, remittent, and undetermined.

These two types are not infrequently observed in an absolutely pure form, so that the fever-curve by itself gives no idea as to the character of the infection. More commonly, however, irregularities are found in the course of the temperature, and they are sometimes so marked that a "type" can be recognized only by a more or less forcible interpretation, or not at all.

The principal reasons for the irregular manifestations of these fevers are found in the following facts: 1. The generations of parasites are less uniform than in the fevers of the first group, as a consequence of which sporulation is completed not in the short period of a few hours, but continues to take place for twenty-four to thirty-six hours. The fever paroxysm is, therefore, prolonged. 2. The evolution of the parasites is not confined within any strict limits, as is the case in the parasites of the first group; on the contrary, there is a marked inclination to hastening of the maturation—in other words, to anticipation. 3. Multiple generations,—although seldom more than two,—as well as mixed infections, are frequent.

When we consider the length of the individual paroxysms, on the one hand, the frequency of multiple generations, on the other, it is readily intelligible why the paroxysms run into one another with the production of continuous fever. The patient is seldom conscious of the individual paroxysms, since they are not ushered in, as in the fevers of the first group, by an unmistakable chill. In fact, it is usually possible to analyze the continued only by frequent taking of the temperature. Moreover, the difficulty is increased by the fact that not every remission can be taken as the close of a paroxysm, for, as we will see, the curve of the simple malignant tertian paroxysm commonly shows a pronounced remission.

It is often difficult and frequently impossible to say if a continued has arisen through prolongation of the paroxysms and anticipation,—and should be designated, therefore, subintrant,—or if an increase of the paroxysms within a given interval had produced a continuity of the fever—in which case it should be regarded as subcontinued.

The blood examination, in cases where the fever-curve is not pronounced, may sometimes give the required information; nevertheless, since we are striving after the greatest possible simplification of nomenclature, we should abandon the difference between subintrant and subcontinued as applied to this group, especially as it would require in every single case a personal and not always successful investigation, in order to determine which was present. Marchiafava and Bignami took the trouble, in a series of cases, to parallel the fever-curve with its parasites, and found that the clinical character of a malignant continued is the same whether the continued is subintrant or subcontinued. The differentiation, therefore, is lacking also in practical value.

It is sufficient for us to know that the continued arises: (1) By a prolongation of the paroxysm; (2) by a prolongation and anticipation; (3) by an increase of the paroxysms, as a result of multiple generations of parasites (seldom more than two); (4) by mixed infection.

Change of type occurs more frequently in these than in any other forms of malarial fever, and its range is from intermittent to subcontinued and vice versâ. In a number of cases the fever begins as an intermittent, quotidian, or tertian. On account of improper treatment, but also in spite of rational therapy, this intermittent becomes remittent or continued. This is sometimes a result of the prolongation and anticipation of paroxysms, but most commonly of the development of a second generation of parasites. Given the opportunity of observing such a case from the beginning, with no pernicious symptoms calling for radical treatment, this transition may be accurately followed, and then the analysis of the fever-curve presents relatively few difficulties.

In other cases—and these are the rule—these infections begin with a remittent fever; more than this, in certain tropical fever regions no other primary infection is known. After several days' duration the remittent, usually as a result of the therapy, begins to show an intermittent type. This is due to the fact that if there are two generations of parasites, one is killed or decidedly reduced in virulence by the quinin, and, as a consequence, one series of paroxysms disappears or is evidently modified. The curve is then considerably simplified and the mechanism of infection made clear.

As to the type of malarial fever in India, Fayrer writes as follows: "Quotidian is, no doubt, the most frequent form, but in my experience the day and hour of recurrence are apt to be most irregular; and were it not that the definite types are most distinctly marked in other parts of the world, designations denoting a certain fixed period would scarcely have been adopted in India."*

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* *Loc. cit.*, p. 318. [We must remember, however, that up to a few months ago under the heading malarial fever large numbers of cases have been included of what we now know to be due to an entirely different parasite, viz., the so-called Leishman-Donovan bodies.—Ed.]

QUOTIDIAN FEVER.

As already mentioned, this may be absolutely regular. The paroxysms last then six to eight hours, with between them a completely afebrile interval (Fig. 29). The paroxysms frequently anticipate, with a consequent deviation from the regular type.

Prolongation of the individual paroxysms for sixteen to twenty-four hours—a result of the irregular congregation of the generations of parasites—occurs very frequently and changes the intermittent to a remittent or continued. In these cases we speak of a subintrant quotidian. Postponing types also occur, especially in fevers that tend to spontaneous recovery.

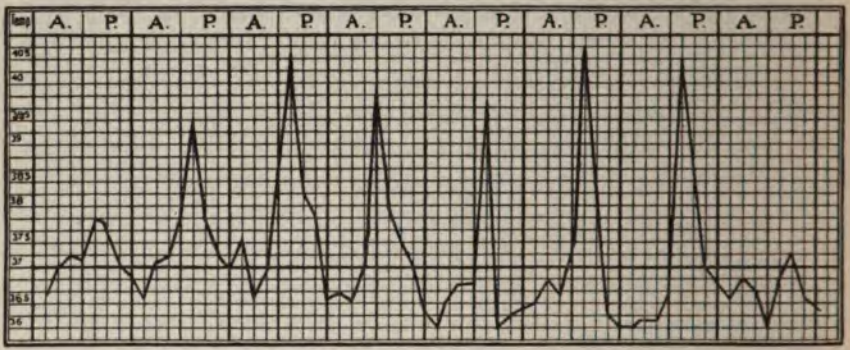

FIG. 29.—QUOTIDIAN (after Marchiafava and Bignami).

MALIGNANT TERTIAN.

The occurrence of a tertian type in severe fevers of a pernicious character was known even to Celsus. In Lib. iii, Cap. iii, of his works he writes: "Tertianarum vero duo genera sunt. Alterum eodem modo, quo quartana, et incipiens, et desinens; illo tantum interposito discrimine, quod unum diem præstat integrum, tertium redit. Alterum longe perniciosus, quod tertio quidem die revertitur, ex octo autem et quadraginta horis fere sex et triginta per accessionem occupat (interdum etiam vel minus, vel plus) neque ex toto in remissione desisit, set tantum levius est. It genus plerique medici appellant."*

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* In another place (Cap. iii) Celsus writes: "At ubi id genus tertianæ est, quod ἡμιτριταιον medici appellant, magna cura opus est, ne id fallat. Habet enim plerumque frequentiores accessiones decessionesque, ut aliud morbi genus videri possit; porrigiturque febris in horas viginti quatuor, et triginta sex; ut, quod idem est, non idem esse videatur."

In later times Ludovicus Mercatus, Physician in Ordinary to Philip II, described especially well "tertiana perniciosa"; he says: "Est itaque perniciosa tertiana febris quædam, quæ, simulata tertiani circuitus, effigie, lethalis et mille accidentibus periculosissimis implicata existit." Torti writes†: "Primo necat hominem perniciosa intermittens, potissimum tertiana." Morton, too, was acquainted with the perniciousness of tertian fevers, and this knowledge was preserved, though only by a few writers. Riehl, for instance, while discussing the epidemic of comatose malaria of the year 1730, described by Werlhof,—and called at that time "deadly fever,"—mentions that the type of this pernicious fever was usually tertian. Josephus Frank likewise asserts that pernicious fever has usually a tertian or quotidian type.

It was only very recently that Marchiafava and Bignami called attention to the almost forgotten malignant tertian fever, and by careful investigation determined it to be the principal one of pernicious fevers. Independently and almost simultaneously with these investigators the author recognized the existence of a tertian fever that was produced by the crescent-forming parasites.

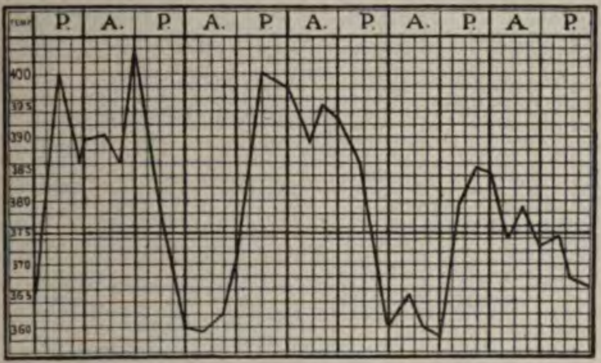

FIG. 30.—MALIGNANT TERTIAN (after Marchiafava and Bignami).

The most striking characteristic of this fever was mentioned by Celsus in the previously quoted short remarks. This consists in the long duration of the paroxysms, which usually lasts thirty-six hours or over. On account of this the period of apyrexia is very short, and usually not at all sufficient for the recuperation of the patient, who, even during this short interval, is, as a rule, considerably prostrated.

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† Lib. iii, Cap. i.

A large number of these cases show a characteristic curve, which has been accurately described by Marchiafava and Bignami, and which I can confirm from my own experience. The peculiarities of this curve (Fig. 30) consist in the following: The temperature rises quickly, frequently without a chill; it remains, with only slight fluctuations, for several hours at this height, and falls at the middle of the paroxysm, but usually not to normal (pseudocrisis); soon after, sometimes accompanied by a chill, there is a new rise, frequently higher than the first, and after remaining a while at this height, it finally defervesces. According to Marchiafava and Bignami, we may differentiate in this curve a rise, a pseudocrisis, a precritical elevation, and a crisis. Nevertheless this curve is not absolutely characteristic of this fever, for, on the one hand, there are a number of malignant tertian fevers which show quite a different temperature movement (Figs. 32, 34); on the other, it occasionally happens in ordinary tertian that the paroxysm lasts for thirty-six hours (Figs. 25, 28), and that the curve shows a pseudocritical decline. Still, what is in one case an exception is in the other a frequent occurrence, or even the rule, and, everything considered, the length of the paroxysm may be designated the principal characteristic of malignant tertian fever.

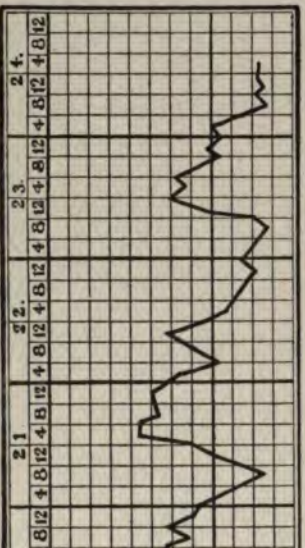

FIG. 31.—MALIGNANT TERTIAN.

It is evident that this fever can and should be called "tertian," since the beginnings of the two paroxysms are forty-eight hours apart. In Italy authoritative voices have been raised against this designation—for instance, that of Baccelli. Instead of malignant tertian, the name biduous was suggested, on account of the fever extending over two days. Even though we must confess that this designation has some justification, is easy to handle, and would prevent misunderstandings, there are still better reasons for the preservation of the historic name, brought recently again into prominence by Marchiafava and Bignami. These reasons are based principally on the fact that all malarial fevers are named according to the duration of development of the parasites causing them.

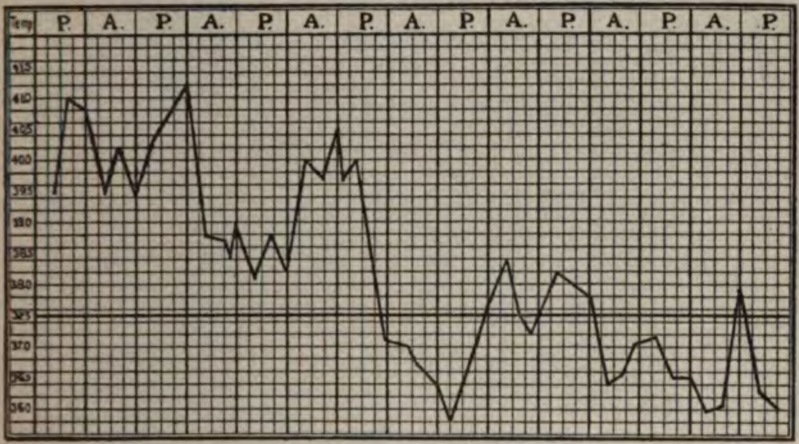

FIG. 32.—MALIGNANT TERTIAN BEGINNING WITH CONTINUED FEVER (after Marchiafava and Bignami).

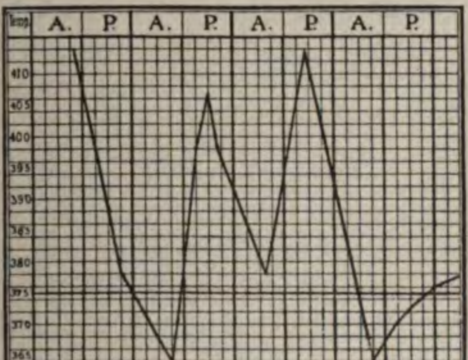

FIG. 33.—MALIGNANT TERTIAN.

Deviations from the typical curve described frequently occur, so that it is often difficult to find the basic type or even an approach to it. Marchiafava and Bignami mention the following abnormalities as frequent: The rise occurs not suddenly, but gradually; the pseudocrisis does not make a remission, but an intermission, so that two paroxysms completely separated seem to have taken place; the duration of the paroxysm increases under marked fluctuations of the temperature; the precritical elevation fails to occur. In the paroxysms as they follow one another we may find the following deviations: Anticipation, postponement, prolongation of the paroxysm with shortening of the apyrexia, light fever movements during the time when there should be apyrexia, and doubling of the paroxysms (tertiana maligna duplex).

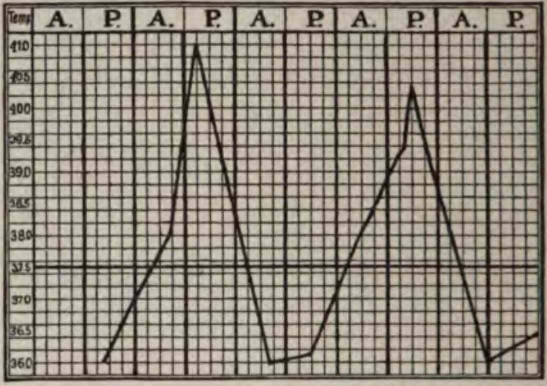

FIG. 34.—MALIGNANT TERTIAN.

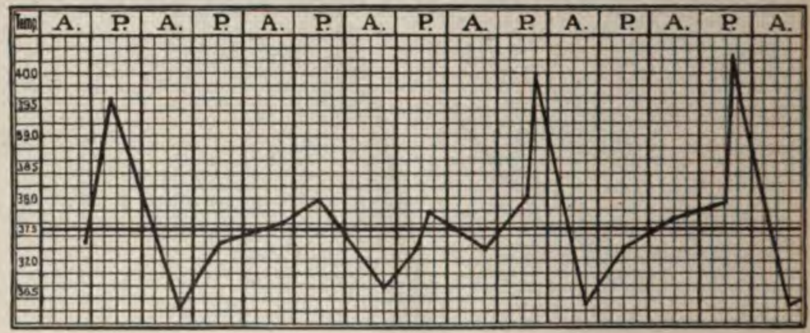

FIG. 35.—IRREGULAR FEVER WITH PREDOMINATING TERTIAN TYPE. On the first two days a few ameboid parasites, later only crescents.

All these exceptions illustrate the difficulties which we meet when analyzing the curves of malignant fever. How these irregularities are produced has been described in another place.

THE ORDINARY SYMPTOMS OF THE FEVERS CAUSED BY THE CRESCENT-FORMING PARASITES.

As has been stated, these fevers present an extraordinary variety of symptoms, in that there is scarcely a system of organs which does not occasionally participate and in a conspicuous way. These symptoms may be the result of the accumulation of parasites in the organs, or of the (hypothetic) intense poison. In the latter case the disease is given a peculiar stamp, which, to the inexperienced, may not at all recall malaria.

We will discuss, first, those cases which show no preponderating participation of any organ and no severe general symptoms; in other words, the simple forms of this infection.

In the milder malarial regions infected with the crescent-forming parasites these simple forms constitute the great majority of cases, and even in the severest malarial regions,—*e. g.*, East and West Africa,—where the cases of the true pernicious variety occur in immense numbers, the simple forms are not uncommon.

The mild fevers of this class have many features in common with those of ordinary intermittent fever (tertian and quartan). But this is true only in the minority of cases. In the first place, the cold stage, which occurs so prominently in almost every case of the ordinary variety, is in these often very rudimentary and not rarely entirely wanting. According to Thayer and Hewetson's statistics, a chill or chilly sensations were found in 71.4 per cent. of cases of the latter: in 97.2 per cent. of cases of the former. As a consequence, the patient frequently fails to realize his elevated temperature, and has no support on which to base the actual beginning of the paroxysm. The sweating stage is less commonly absent, even though it is not so regular as in the intermittent fevers of the first group.

The disease usually begins suddenly, though sometimes with vague prodromal symptoms. The first symptoms often consist in headache, a tired feeling in the limbs, sciatic pains, and absolute anorexia, frequently associated with vomiting. The patient appears in the majority of cases anemic, with somewhat of a subicteric discoloration. The lips are dry; the tongue, thickly coated.

The sensorium is often unaffected, and the patient gives then the impression of a hectic consumptive; sometimes a mild stupor or slight delirium exists. During the short apyrexia the patient is not restored to that complete euphoria that we see in fevers of the first group. Though patients of the latter class feel somewhat weak and in need of rest, they are otherwise well and manifest a good appetite and good spirits; while the patients under consideration, even during the interval, are severely depressed, if not prostrated, incapable of physical or mental work, and complain of painful sensations in the limbs and head.

As to the type of fever, we need only say that it manifests the same variations in the light forms as in the severe; in other words, it is not a criterion of the other symptoms. The tumor of the spleen is evident, even in the first days of the disease. The anemia progresses more rapidly than in fevers of the first group.

Quinin is usually successful,—at least, the paroxysms are promptly modified after its administration,—though in spite of energetic treatment relapses are not prevented.

In many cases severe symptoms are manifested by the gastrointestinal tract. These cases are described under the special name gastrobilious, bilious remittent, or jungle fever. Little known in Europe, this form is the most frequent expression of malarial infection in tropical and subtropical regions. It is recognized on all coasts of the Mediterranean Sea, especially Italy, Sicily, Algeria, Egypt, Greece; it is especially frequent in India, in the United States of North America, particularly in the southwestern parts of the Union (Wood), and is wide-spread in Mexico, Brazil, and in the Antilles. It is likewise very frequent on the east and west coasts of Africa as well as in Madagascar.

Since we will return to the description of the severe bilious fever in the section on Pernicious Fevers, we will content ourselves here with a short description of the milder symptoms. They are as follows:

The loss of appetite is absolute and is frequently associated with a decided distaste for every kind of nourishment. The patient is tormented by a nauseating taste, and the tongue is thickly coated and swollen. In addition there is vomiting. The vomit is at first greenish, later yellowish, and finally almost pure bilious, when no more hydrochloric acid remains in the stomach. The vomiting is extremely tormenting and frequently uncontrollable, ceasing only with the intermission or remission of the fever.

The epigastrium is often distended and sensitive to pressure. There may be slight meteorism. There may be either constipation or diarrhea. In the latter case the stools are dark and rich in bile-pigment; rarely the opposite. From the beginning there is a subicteric discoloration, which may increase to intense jaundice.

The urine is dark, concentrated, and contains considerable urobilin when jaundice exists. Bilirubin may be found; likewise albumin. The other symptoms are the same as have been described for the ordinary fevers of this group.

The prognosis is good, though it must be remembered that severe complications can never be excluded. When the case is left to itself, we occasionally see spontaneous cure, in five to ten days, though it is always advisable to push from the beginning the specific and symptomatic treatment.

PERNICIOUSNESS.

It was the custom of the old writers to differentiate among the malarial fevers pernicious forms. This custom has been continued, and though it no longer has the justification that it had, for instance, in Torti's time, it will probably be prolonged for some time into the future.

By the expression "pernicious fever" we understand one directly threatening to life. This must not be the result of the occurrence of a second disease,—in other words, a complication,—but the malarial fever itself must be responsible for the dangerous symptoms.

We search pathology in vain for an analogy. As far as I know there is no other disease, though it runs its course sometimes smoothly, and without prognostic danger, again under the severest and most threatening symptoms, for which a division into benign and pernicious has been made. If we were to follow out this division, we should speak of a benign typhoid fever when the disease was mild, of a pernicious typhoid fever when, in its evolution, dangerous symptoms arose. There would be, in addition, an endless series of subdivisions, depending on whether the dangerous symptom proceeded from one or another organ. The same scheme might be carried out also for all other diseases that terminate not necessarily fatally or in recovery. Difficulties would naturally not be wanting, for not all physicians would be unanimous as to what symptoms should be considered pernicious.

There is nothing further from my mind than the thought of reproaching the old writers, of whom especially Torti stands out immortal for introducing the notion of pernicious fevers. If we think back to that time when the most primitive pathologico-anatomic and etiologic knowledge was wanting, we see at once that besides the symptoms apparent to the senses, it was the severity of the symptoms which acted as the most important basis in the classification of diseases. With the further development of knowledge, for which we must thank the genius and diligence of generations, our foundation has been broadened. The occasional severity of a disease, though it must be taken into consideration for the sake of the patient, is evidently useless as the basis of a scientific classification It is possible that the future may so solve the question that from the individual susceptibility and the toxicity of the parasite the appearance or non-appearance of dangerous symptoms will be prognosticated with astronomic certainty. A beginning has already been made in the recognition of the facts that the parasites of the first, no matter how strong or numerous the generations, scarcely ever produce pernicious fever, and that perniciousness is almost exclusively confined to the infections caused by parasites of the second group. Further than this we cannot go at the present moment, and we must take the group of infections caused by crescent-forming parasites as a whole and say that they are sometimes mild, sometimes severe, under circumstances even fatal, as is the case in many other infectious diseases.

Although we have established the fact that a classification on the basis of the severity of the symptoms is not scientifically justified, we must add that the most thorough analysis of the severe symptoms is a primary essential.

For this reason we shall first consider the question: Of what kind are the pernicious symptoms? Even the answer to this primitive question raises difficulties, since there are very few symptoms which, without argument, can be looked on as dangerous to life. I will say at once, in order not to pick the matter all to pieces, that we will consider the word "pernicious" in a broad rather than a narrow sense, and include under it not only the symptoms directly threatening life, but all that may be considered dangerous or even severe.

The pernicious symptoms may be associated with the nervous system, the vascular system, the gastro-intestinal tract, the genito-urinary system, the spleen, and, in rare cases, even other organs. In a large number of cases it is the whole organism that produces the general impression of a status perniciosus without any definite local symptoms, though again there are cases in which several organs, as, for instance, the nervous system and the intestinal tract, either simultaneously or alternately, present the pernicious symptoms. It is especially this last that makes a division of these forms so difficult from a clinical standpoint; yet certain groups of symptoms are repeated so frequently that a separation of these into types is clinically justified, especially since we are in a position to handle them in no other way.

As regards the **frequency** of pernicious fever, statistics are almost unavailable, for the reason that every physician and every malarial region has a different conception of the word "pernicious." Still there is no doubt that in certain "severe malarial regions" more pernicious cases, *sensu strictiori*, occur than in others, even when the latter show just as frequent infection with crescent-forming parasites. It is, moreover, generally recognized that the number of pernicious fevers varies in different years.

Colin states that in 1864 the French Army of Occupation at Rome showed a proportion of pernicious to ordinary fevers of 1: 25. In the same year the civil population of Rome showed a proportion of 1: 20. Laveran observed in Constantine (Algeria) a proportion of not more than 1: 35–40. According to Galvagno, there were treated in the Clinical Hospital in Catania, in the years 1893 to 1895, 1022 cases of malaria, of which only four were pernicious, while in Kamerun, Albert Plehn observed a proportion of 1: 8.5; Frederic Plehn, 1: 11 or 12. Schellong, at Finschhafen (Kaiser William's Land), had 7.3 per cent. mortality; Martin, in Deli (Sumatra), had, on a tobacco plantation worked by Chinamen, over 80 deaths among 200 laborers.

Borius found in Sénégal that the majority of pernicious cases occurred in new arrivals and individuals who were in the tropics over thirty-six months. He stated that, among 100 malaria cases, 4.1 per cent. were pernicious, and these were divided so that in the month of June there occurred 0.9 per cent.; in September, 6.3 per cent. In the years 1863–1872 there occurred, among the 16,366 men in the garrison, 600 pernicious cases.

Pernicious fever occurs in all malarial regions only in the hot season, and especially between the rainy and the dry season. In southern Europe, as well as in Algiers, it is the months July to November that show the most cases.

The different pernicious symptoms occur with varying frequency. In the majority of malarial regions the severe general and the nervous symptoms are the most common. In certain places, like, for instance, tropical Africa, the hemoglobinuric form predominates.

Different factors, sometimes acting alone, sometimes together, seem to be necessary for the origin of the pernicious symptoms, though we must insist that many of these factors are unknown and that in individual cases it is often impossible to say how the severe symptoms originated.

The factors which are at present considered as especially responsible for perniciousness are the following: (*a*) Individual predisposition; (*b*) peculiarity of the parasite; (*c*) anatomic lesions.

Individual Predisposition.—The majority of writers are unanimous in affirming that certain individuals or that an individual at a certain time manifests an especial susceptibility to pernicious malaria. There are people who, as often as they are attacked with malaria, show every time a severe form (sometimes the same, again a different one). It may be that these people, as a result of organic peculiarities of a chemic or anatomic nature not yet recognized, possess something that assists the development of the parasite or its toxin, or that permits the local accumulation of infected blood-corpuscles in certain important capillary regions.

There are others who show a temporary—therefore, acquired—predisposition—for instance, alcoholics, convalescents, or persons enfeebled by heat, overwork, or insufficient nourishment.

It has been observed that an extra effort on the part of a certain organ immediately preceding the outbreak of the malaria leads to a pernicious case manifesting symptoms from this organ; or that a local susceptibility is grounded in an organ weakened by previous disease and transformed into a *locus minoris resistentiæ*.

Baccelli observes that farmers working in the heat of the sun and alcoholics suffer uncommonly frequently from forms associated with coma or delirium, while people with intestinal catarrh are attacked by the choleraic form.

It has been further recognized that strangers not accustomed to the climate suffer relatively more frequently from pernicious fever than the native inhabitants. According to Borius, the native adult blacks in Sénégal seldom manifest it. Some writers (Rho) observed that at the beginning of a hot season persons who never before had malaria are attacked by severe symptoms, even when the blood examination shows a comparatively small number of parasites. This would seem to indicate a special susceptibility. Finally those cases are also attributable to individual predisposition which begin mildly but take on a pernicious character as a result of improper treatment.*

As to the **peculiarities of the infecting parasite,** only the small parasites come into consideration in the genesis of pernicious fever. Infections with parasites of the first group run always a mild course. This alone is very significant of the possession by the parasites of the second group of certain specific properties.

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* The fact that the small parasites cause pernicious fever much more frequently in the tropics than in the temperate zone is probably due to the enfeeblement of the organism by the climatic conditions, by which a temporary individual susceptibility is created. Otherwise we would be obliged to assume that the small parasites were endowed with different toxic and pathogenic properties in different parts of the world, and for this assumption we have no foundation.

Moreover, of this group it is especially the malignant tertian parasites that, according to Marchiafava and Bignami, produce pernicious fever.

When we consider the factors that may be responsible for this tendency to malignancy, the following present themselves: (1) Their number; (2) their toxicity; (3) their power of resistance against medicaments. Besides these three factors there are others which we will take up later.

The number of parasites in pernicious cases is usually extraordinary. In an unstained preparation from the blood of the finger we frequently see a very large number of infected erythrocytes, but when we make sections of the internal organs, especially the brain, the spleen, etc., this number is discounted. Moreover, it sometimes happens that the peripheral blood is very poor in parasites, when that of the internal organs swarms with them. In cases of infection with crescent-forming parasites, therefore, nothing can be concluded from the ordinary blood examination as to the numbers that may be present. Whether the number of parasites in the pernicious cases is much larger than that of the parasites of the first group in high grades of infection with them is a question which at the present time can be answered only approximately, since, as far as I know, no actual counts have been made. From the general impression which I have obtained, naturally only from the peripheral blood, the number in malignant fevers is perhaps larger, yet the difference scarcely seems so decided as to make this factor alone responsible for the perniciousness.

Why in one person the malignant parasites should increase but little, in fact, occasionally even disappear spontaneously, while in another they increase to extraordinary numbers, is a problem that must be referred to the causes of perniciousness in general, namely, the personal susceptibility of the affected individual and the proliferative activity of the parasites.

Yet it may be regarded as settled that, *ceteris paribus*, an infection with a large number of malignant parasites is more severe than one with a smaller number.

There are apparent individual exceptions to this rule—for instance, Baccelli has reported cases of pernicious fever where the number of parasites was small. But in these cases only the peripheral blood was examined, which, as mentioned above, cannot be regarded as a criterion. In other cases where there are no parasites or their number is small and yet the pernicious symptoms continue, we must consider the possibility that the parasites may have been killed by the quinin, but that the organic changes produced by them or their toxin (for instance, degeneration of the endothelium of cerebral or renal vessels, or small hemorrhages in the brain substance) are so advanced as to be able to continue the symptoms of the disease.

The toxicity of the malarial parasite is an assumption, though, according to our way of thinking, a justifiable one. Moreover, it is not without reason that we attribute a greater toxicity to the malignant parasites than to those of the first group. As we have shown, the difference in numbers is not sufficient, therefore we must bring into question the toxicity. This is not necessary in all cases, for there is no doubt that a great number of the pernicious symptoms may be explained on purely mechanical grounds, yet there always remain certain symptoms which cannot be explained in this way—for instance, the malarial or postmalarial hemoglobinuria and the necrotic changes in the renal epithelium found by Bignami. These, for the present, must be attributed to the action of the toxin.

The effect of quinin on the parasites varies, probably because the vitality of the parasites is not always the same. In one series of cases the small parasites disappear on relatively small doses of quinin as promptly as or even more so than benign parasites ordinarily do; in others they manifest an especial obstinacy to treatment. True, certain forms—the crescents and their spheres—are absolutely indifferent to quinin, but this is of little importance since the crescents usually have nothing to do with the acute symptoms.

The **histologic findings** are usually sufficient to explain the majority of the pernicious symptoms. These histologic lesions consist principally in the occlusion of vessels by infected erythrocytes (Frerichs, Laveran, Guarnieri, Bignami, Marchiafava), and depending on the organ in which the capillaries are occluded, one or another symptom may be manifested. Additional details in relation to these findings will be given in the section on Pathologic Anatomy. Here we only desire to call attention to the fact that it is exactly the cases of infection with the malignant parasites that show these accumulations in the smallest vessels. The reasons for this can only be conjectured, not proved. It cannot be, for instance, that the blood-corpuscle is carried less freely by the blood-stream on account of the increase in weight produced by the parasite, because in this regard there is no difference between the benign and malignant parasites, and if there were a difference, it would be in favor of the former, which are much larger and therefore probably heavier. Further, the blood-corpuscles infected by malignant parasites are usually somewhat shrunken, and should consequently pass through the capillaries more readily. Possibly it may be a sort of agglutination, either as a result of roughness or adhesiveness, that holds the infected erythrocytes to the vessel-walls. As a matter of fact, we have more than once observed in unstained preparations under the microscope that the infected blood-corpuscles do not swim in and out of the field division like the non-infected—in other words, they appear to adhere more to the glass.

In addition to the occlusion of vessels in the brain we find punctate hemorrhages as a direct result of this occlusion, which may produce and continue the pernicious symptoms.

A much-discussed question is, whether the fever itself may produce the perniciousness; in other words, is there any type which *eo ipso* necessitates perniciousness?

In answer to this we may say, first, that pernicious symptoms occur in strictly intermittent as well as continued fevers. More than this, they may occur, even though seldom, without any fever (latent pernicious). These facts are already sufficient to prove that at least perniciousness is not associated with any definite type of fever, though experience shows that the majority of pernicious cases manifest a subcontinued fever. Baccelli saw, among 356 pernicious cases, 193 with subcontinued fever, and not without reason drew the conclusion that the subcontinued pernicious fever is pernicious on account of its type.

In spite of the frequency of the subcontinued type in pernicious fevers the endeavor to make this a basis of classification has not met with success.

It is readily conceivable that pernicious symptoms accompanying an intermittent fever would usually show a different character to those accompanying a continued fever. In the former, so-called culminating symptoms (coma, eclampsia, hemiplegia, aphasia, hemoglobinuria, etc.) occur, which may be truly pernicious or indifferent, depending on whether they proceed from a very important or less important organ (these are the comitatæ of Torti). In the latter, these culminating symptoms may also appear, but this is not the rule; on the contrary, the fevers extending over several days usually give rise to a symptom-complex which includes the whole organism and frequently imitates that of other diseases (solitariæ of Torti).

Baccelli correctly points out that an individual personal factor participates in the culminating symptoms of the comitatæ, which is not the case in the solitariæ.

Yet, all in all, it may be considered settled that the perniciousness is associated with no definite elevation of temperature and no particular type of fever.

The pernicious symptoms seldom occur at the beginning of the malaria—Laveran observed no such case among all his rich material; on the contrary, they usually appear only after the intermittent or continued fever has lasted some time, though in any case they may break in very unexpectedly.

Especially in old people does it frequently happen that the disease, after progressing under apparently mild general symptoms and slight fever, suddenly manifests pernicious symptoms (most commonly coma) that are rapidly fatal. In these cases the blood examination is of great prognostic value.

A fever with pernicious symptoms may sometimes recover spontaneously. There are especially numerous cases of repeated hemiplegic, aphasic, hemoglobinuric, a less number of comatose attacks known, which recovered without treatment. Still these are always exceptions and do not relieve the physician from the duty of beginning specific treatment at once, and ordering a change of climate if a severe infection with malignant parasites is confirmed or threatening symptoms are present.

In the following we give a description of the more frequently observed types of pernicious cases, once more insisting that we employ the expression "pernicious" not in the sense of dangerous to life, but in the broader sense of general seriousness.*

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* Torti divided the pernicious fevers in the following way: "Quod si lubeat melioris ordinis gratia hasce varias perniciosarum febrium differentias ad terminos scholarum, et ad peculiarem Categoriam reducere, in promptu erit, supposita generali intermittentium omnium tum simplicium, tum duplicium, tum triplicium divisione in Benignas et Malignas, istas item subdividere in Comitatas ferali aliquo symptomate verum morbum simulante, immo et æquante, adhuc tamen intermittentes, et in Solitarias, seu nullo peculiari symptomate, sed potius multiplici, et vario comitatas, et ex dispositione intima in continuitatem, atque, et vocant, acutiem quammaxime proclives. Comitatas adhuc intermittentes rursus subdividemus habito respectu ad conjunctum symptoma, in Colliquativas et Coagulativas, ut continuarum etiam malignarum mos est. Ad Colliquativas erunt referendæ quatour priores species enumeratæ, quas mutuato nomine ab ipso symptomate vocabimus: I. Cholericam vel Dysentericam; II. Subcruentam vel Atrabilarem; III. Cardiacam; IV. Diaphoreticam. . . . ad easdem vero Coagulativas revocabimus tres posteriores species, videlicet: I. Syncopalem; II. Algidam; II, Lethargicam. Et sic primum membru propositæ divisionis explebimus. Quo ad

TYPHOID PERNICIOUS MALARIA.

(Syn., Perniciosa Typhosa; Subcontinua Maligna; Subcontinua Typhosa; Accès Pernicieux avec état Typhoïde.)

By typhoid pernicious we understand those cases of malarial infection the general appearance of which recalls typhoid fever. Among the symptoms of typhoid fever it is especially the stupor, the clouding of the sensorium, that is meant, and since the word *στῦφος*, a cloud, exactly expresses this stupor of the intellect, the designation has an etymologic justification. We must confess that by this description no sharp limitation of a definite series of cases is made, and that cases not infrequently occur which would be designated as typhoid by one physician and not by another. Still we may suppose a similar conception in the great majority of cases, for exactly the same differential diagnostic difficulties are present which before Laveran's discovery could be decided only by the autopsy.

It would be a mistake to believe that typhoid pernicious malaria showed always the same picture. Almost exactly the opposite is the case. No other clinical form of malaria shows such a variety of symptoms or would suffer less a schematic representation.

The disease may manifest all its symptoms from the beginning, or be preceded by a few prodromes, or again it may begin as a moderately severe or even mild form of malaria and take on its typhoid character on the third to the fifth day.

The disease may attack those who have never before suffered from malaria, as well as those who have undergone repeated attacks. Yet the latter appear to possess a greater susceptibility, possibly on account of their weakened anemic condition.

The disease frequently begins without a chill, though in other cases this may be present. Moreover, in the course of the disease chills and horripilation may occur.

The principal complaints of the patient are headache, backache, general weakness, restlessness, loss of appetite, thirst, and vomiting. The headache consists sometimes in a tormenting sensation of pres-

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aliud vero membrum ejusdem divisionis, in quo collocavimus Intermittentem nullo peculiari, distinctoque symptomate comitatam (quam idcirco Solitariam diximus) sed ex natura sua in continuitatem, atque acutiem valde proclivem, hanc sub una tantum specie reponemus, cujus tota ratio erit hæc ipsa, quod ad continuam essentialiter et acutam tendat, licet inde in innumeros differentias accidentales (quotquot scilicet sunt accidentales omnes febrium continuarum differentiæ) possit subdividi, et Subcontinuam simpliciter nuncupabimus."

sure over the frontal or temporal region; again, of neuralgic pains over different parts of the head. There is more or less stupor, associated sometimes with a tendency to somnolence, again to muttering delirium. The patient sometimes talks in a half-loud tone about circumstances connected with his avocation and about things in which he is interested; again he manifests marked excitement in the form of violent delirium, gesticulation, crying, attempts at escape, and more than one of these patients, in an unguarded moment, has thrown himself from the window. The patients often appear as if devoid of intelligence, idiotic, and laugh stupidly. Many cases show an obstinate insomnia, uncontrollable even by large doses of chloral; others again sleep heavily and must be roughly summoned in order to take nourishment, etc.

Secessus involuntarii, on the one hand, retention of urine, on the other, is not rare. A gradual sinking into coma is not uncommon, though this is usually transitory, except where it occurs as an antemortem symptom.

In the general behavior the great restlessness is striking. Patients are continually changing their position in bed, continually abandoning one position for another, without reason. The Romans designated this restlessness "jactationes."

The expression of the face, corresponding to the condition of the sensorium, is variable, though the face always shows characteristic signs of serious disease on account of the anemia and melanemia, to which are often added a slight degree of jaundice and feverish redness. The lips are dry, covered with crusts, and frequently show a slight tremor. The tongue is dry, heavily coated, fissured, swollen, and is protruded tremblingly. If the disease continues some time, especially in the case of a relapse, edema of the feet may occur.

The skin is at different times dry and covered with perspiration; its color is grayish yellow. Herpes, urticaria, and sudamina are frequently seen, and some writers (Negel) claim that they have observed roseola.

The fever may be intermittent or subcontinued (remittent); it may even be quotidian or tertian, though frequently no type can be determined.

In the majority of cases the fever paroxysms are of long duration, extending over thirty-six to forty-eight hours, and there are physicians who, on this account, describe the fever as continued. Still, from Celsus down the excessive length of the paroxysm in the severe estivo-autumnal fevers has been recognized, and the fevers called intermittent; we may, therefore, continue to call them intermittent, even when the fall of temperature occurs only after forty-eight hours. These are cases of simple malignant tertian. The symptoms of typhoid pernicious may also be associated with the quotidian type, though we usually have to do in these cases with subintrant fever. This shows a markedly dentate curve with a daily rise and a daily remission.

If the symptoms of the disease are associated with intermittent fever, some of them retrogress with the intermission, to become conspicuous again with the rise in temperature, while others continue throughout the short apyretic interval. The latter is especially true of the stupor, the dry tongue, and the general weakness.

A subcontinued type of fever is more frequent in this condition than an intermittent type, and some writers (for instance, Baccelli) speak, therefore, of a typhoid subcontinued. Since the same symptom-complex occurs in both, I prefer to retain the general name, typhoid pernicious, than change it for this narrow one.

At the beginning of the disease intermittent paroxysms may occur for several days, which, by prolongation or doubling, may eventually produce a subcontinued fever. This commencement with intermittent paroxysms possesses some diagnostic value when there is a question of typhoid fever, though this value is limited, since the disease may begin as a subcontinued fever and since there are not rare cases of typhoid fever which begin as intermittents.

The fever-curve of a subcontinued for one or two weeks will sometimes show the original type,—whether tertian or quotidian,—though in a majority of cases this is not decisive. In addition to the spontaneous temperature fluctuations, which are difficult to recognize, there are others due to the quinin (administered necessarily from the beginning), and this may alter the curve in such a way that it is impossible to come to any conclusion.

The fever may end by crisis or by lysis. It is not rare to see a subcontinued under the influence of quinin give way to an intermittent, and after several paroxysms, cease. Hyperpyretic temperatures—over 42°—are occasionally observed, but they are not at all characteristic of pernicious typhoid.

Subnormal temperatures are sometimes seen during the intermission. Several days of subnormal temperature sometimes follow one another, during which time the symptoms not only do not improve, but, if possible, become worse. Under these circumstances we speak of an adynamic form.

The pulse, as a rule, corresponds to the temperature: it is often dicrotic and of low tension. In severe cases, especially in the adynamic forms, the pulse becomes thready and its tension is reduced to a minimum. This may occur even during the period of apyrexia.

Baccelli, the rales are found not like in typhoid, over the posterior inferior parts, but irregularly localized. According to the same writer, these catarrhal symptoms may disappear unexpectedly, to recur in the same way.

Dyspnea is frequent and may sometimes be marked. A dry cough is likewise common. Not rarely the patient is tormented with a singultus that may continue several days and cease suddenly without known reason. The singultus may also intermit with the paroxysms. Epistaxis for one or more consecutive days is not infrequent.

The urine is usually concentrated, rich in urobilin, and contains frequently albumin, and not rarely, even though it is only transitory, small amounts of hemoglobin in solution (Kelsch and Kiener). The blood shows the signs of anemia and melanemia, often to a marked degree.

In all stages of the disease small ameboid parasites are usually found in the blood. They are sometimes non-pigmented, but again contain a few dust-like pigment-granules, or, when more advanced, a large dark pigment clump. The infected corpuscles are sometimes shrunken, making the so-called brassy corpuscles. Sporulation forms are rare in the blood from the finger. The parasites are in the same stage of development, showing that they belong to one generation only in cases with intermittent fever. Examining such cases before the paroxysm, we see a relatively large number of pigmented parasites; at the height of the paroxysm, only the young, very small, ameboid organisms.

In the majority of cases, especially in those with subcontinued fever, we find all possible stages of development, so that it is impossible to speak of generations. Maturation and sporulation are continually occurring. The battle, which in the intermittent fevers is limited to a certain period, continues here without cessation, while the enemy continues to throw new forces in the form of spores into the field.

If the disease has existed some days, or if we have to do with a relapse, crescents or spheric organisms of that class are always present. The latter are frequently flagellate. Melaniferous leukocytes are frequent in all stages of the disease.

At the termination of the disease the ameboid forms disappear or at least diminish in number, while the crescents remain for a long time. It sometimes happens that the parasites disappear, at least from the peripheral blood, and yet the symptoms continue to progress (Marchiafava and Bignami).

The duration of typhoid pernicious is variable. It may be three to four days or two to three weeks. It is usually influenced by rational therapy, and since the introduction of the "divine bark" (göttlichen Rinde), the cases of short duration are by far the most frequent. Yet even to-day, in spite of quinin, long-lasting and fatal cases occur.

The course may be spontaneously favorable, yet it would be a serious error to build on this possibility and forego the specific therapy.

According to Kelsch and Kiener, the mortality in typhoid pernicious is 10 per cent.; in the adynamic variety (see below), 25 per cent. Werner gives the mortality for the first form as 0, for the latter, 6 per cent. How much of this striking statistical difference is to be reckoned to the difference in the local "genius epidemicus" in Algeria and Russia, how much to the difference in the classification of the cases, cannot be estimated.

The *exitus letalis* is usually ushered in by coma of short duration, yet it may appear unexpectedly.

During the course of the disease different culminating symptoms —coma, convulsions, hemoglobinuria, edema of the lungs, hemorrhages, algor, etc.—may appear, to disappear again or produce rapid death. Expressed in Torti's fashion, these would be complicating symptoms in the course of a solitary fever. To describe all the possibilities and occurrences is not in the realm of this work.

The **diagnosis** of the pernicious typhoid form is readily made from the blood examination. Before Laveran's discovery it was exceedingly difficult for a physician in a malarial region to make a positive diagnosis, especially in the first days of the disease, between typhoid fever and pernicious malaria. From the melanemia alone the diagnosis is not sufficiently positive, since it might easily happen that in the small amounts of blood which we can examine under the microscope no pigment would be found. The parasites, on the contrary, whether pigmented or non-pigmented, are met regularly and at all times; they are, therefore, an absolute criterion of inestimable diagnostic value.

Before the parasites were discovered the clinical symptoms and the result of the treatment with quinin made the basis of the diagnosis. It was a magnificent achievement of Torti's to recognize this method of diagnosis in the action of Peruvian bark. This criterion (*ex juvantibus*), which we are obliged even yet to apply in other cases,—syphilis, articular rheumatism,—on account of ignorance of the causal agents, has been adhered to up to the present time by physicians who are unacquainted with the malarial parasites or who refuse to recognize them. There can be no doubt that the diagnosis of malaria, *ex juvantibus*, led to a correct conclusion in innumerable cases, but it is likewise certain that it led, too, to innumerable errors, for malarial fever does not always react to quinin,—and this is especially true of the typhoid pernicious form,—and not every disease that improves after its administration can be regarded as a positive malaria.

The clinical symptoms have proved themselves to be even less practical than the quinin reaction, although numerous clever, observing clinicians used every effort to determine the differential diagnostic symptoms between typhoid pernicious malaria and typhoid fever. The number of these symptoms is so great as to discourage at the onset. Whoever has seen many cases of typhoid fever knows that this classic disease often refuses the frame made for it by the text-books. Taking many cases together and drawing from them the most frequently occurring symptoms, a typical typhoid may be constructed that has a certain didactic and scientific justification that is even necessary, though it aids little toward a diagnosis of individual cases. In addition, typhoid fever often runs a different course in the tropics to that in the temperate zone, on account of the frequent manifestation of symptoms (coma, algor, etc.) which recall severe malaria.

The difficulty of making a differential diagnosis between these two diseases on a purely symptomatic basis is well demonstrated by the outcome of Colin's work. This accomplished clinician, who understood the symptomatology of typhoid and malaria in a way scarcely even equaled, was eventually obliged to conclude that remittent malaria may be "transformed" into typhoid fever.

The following are the principal points which Baccelli, who was thoroughly grounded in the subject, makes in the differential diagnosis*:

TYPHOID SUBCONTINUED MALARIA.	TYPHOID FEVER.
Begins frequently as an intermittent.	Begins as a progressive remittent.
The remissions are very irregular.	The remissions occur regularly in the morning. The temperature rises in the evening, usually about 2°, falls the next morning about 1°, etc.
The temperature may reach 40° the first day.	The temperature does not reach 40° before the third or fourth day.
Headache at the beginning is rare; when it occurs, it is of a pulsating, neuralgic character, and is variable in its location and intensity.	Persistent frontal headache of a boring character from the beginning.
Eyes heavy from the beginning; subicteric.	In the first stage, eyes glistening.
Stuporous expression of countenance, dry tongue, sordes on the teeth, though not marked.	The same symptoms marked.

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* This table has been taken from Rho's treatise.

Typhoid Subcontinued Malaria.	Typhoid Fever.
The odor of the breath is nauseating.	The odor is that of mice.
Delirium may exist from the beginning. It recurs with the exacerbations of temperature and the corresponding symptoms, though it may be replaced by other severe symptoms.	Delirium appears only after the disease is well advanced; is permanent and varies only in intensity.
When pulmonary congestion occurs, the symptoms come on suddenly. The disease foci change their place, are sometimes in one, again in another, lobe, sometimes in one, again in the other, lung. They may disappear and recur with altered intensity. Dyspnea is marked. Circulatory disturbances are present to the end.	The pulmonary congestions develop gradually and are always hypostatic (behind and below); dyspnea is less marked, appears later, and is dependent more on abdominal conditions (meteorism, etc.).
Restlessness and an indefinable desire for change (*jactitatio corporis*) are conspicuous.	Somnolence, prostration, and stupor (*στῡφος*) are prominent.
Meteorism, gurgling in the ileocecal region, may occasionally occur; diarrhea is slight or absent, and has not the same character as that of typhoid.	Meteorism, gurgling, diarrhea, come on gradually and develop to a marked degree.
Participation of the liver frequent; evident subicteric discoloration; often mild jaundice.	Participation of the liver less evident; no jaundice.
Runs no definite course.	Has a characteristic course, which is almost always evident.
Occurs where malaria is endemic, especially in the country; is seldom seen epidemically.	The disease occurs especially in cities, and is frequently epidemic.

Looking over these differential points, we must confess that they contain all the "typical" signs of the two diseases, and yet every one who has had any considerable experience with one or the other disease must acknowledge that he has seen a number of cases where they would not apply.

Fortunately, by the discovery of the malarial parasites, on the one hand, the Gruber-Widal reaction and the bacteria of typhoid fever, on the other, we have grown out of these clinical considerations and are in a position to make the diagnosis of malaria usually after one look into the microscope.

The **prognosis** depends on the individual condition of the patient. Alcoholics, persons with nephritis, arteriosclerosis, and other chronic diseases, as well as the badly nourished, are in more danger than the robust and healthy. The condition is especially dangerous in old age. Otherwise the mortality fluctuates according to the place and time.

Relapses.—Like all the fevers caused by the small parasites, typhoid pernicious shows a marked inclination to relapse. The relapse may repeat again the typhoid character, and it sometimes happens that one person goes through the same form three or four times in one year.

Convalescence is more smooth and rapid than after typhoid fever. After one or two weeks, sometimes earlier, patients are completely recovered, excepting naturally what general disturbances may have taken place.

The following case of a very severe form of typhoid pernicious has been taken from Colin's book (p. 273)

Barbier, a fusileer in the Nineteenth Regiment, aged twenty-two, for eleven months has lived in the Salara quarter (probably the most dangerous in Rome). On August 3, 1864, he was brought to my division, Saint Andre, with the symptoms of a moderately severe remittent: headache, flushed face, warm skin, coated tongue, marked thirst, restlessness, and vomiting. He was ordered 2 gm. pulv. ipecacuanhæ, 1.0 quinin sulphate, to be taken at 3 o'clock, and these were taken in my presence during the afternoon visit.

August 4: Continuation of the same symptoms. Was very restless during the night. During the visit epistaxis (seidlitz powder and 0.6 quinin sulphate).

August 5: Renewed epistaxis, pulse dicrotic, tongue dry, diarrhea, light meteorism.

On the following days the fever and diarrhea continued, with an increase in meteorism; the delirium became continuous, and on August 9 disseminated dry râles were noticed over both lungs.

August 12: Eruption of innumerable, almost confluent, sudamina; subsultus tendinum, irregular unequal pulse, secessus involuntarii.

August 14: At the morning visit the patient appeared somewhat better and answered readily several questions; yet the following night he was seized with convulsions, and the next day, August 15, we found him with head retracted, lips and face cyanotic, and thorax prominent and motionless; in other words, in a state of almost complete asphyxia, as a result of the tetanic contractions of the thoracic muscles (an actual paroxysm of tetanus). In spite of immediate inhalations of chloroform and sinapisms to the extremities and thorax, he died on August 15, at 10 A. M.

*Autopsy.**—The bronchi filled with froth. On the anterior surface of the heart, one ecchymotic spot. No intestinal lesions. The spleen was enlarged to about three times its normal size, was extremely soft, dark in color, and when examined microscopically, showed an enormous number of pigmented organisms of different kinds.

We have detailed examples of mild infections with typhoid symptoms on pp. 74, 75, 79.

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* Here given in abstract.

Some writers differentiate an adynamic form of typhoid pernicious. These cases are characterized by subnormal temperatures, associated with the continuance of the severe prostration. The apathy of the patient is especially striking. He lies devoid of intelligence, with wide-open eyes, giving either no or an unintelligible random answer to questions, occasionally laughing idiotically. He is often too weak to sit up, and if the limbs are elevated, they fall back lifeless. Swallowing is difficult.

Icterus, severe anemia, leukocytosis, and hemoglobinuria are often present (Kelsch and Kiener). The pulse is extremely small and weak. The adynamia occurs most frequently in persons who have become severely anemic on account of preceding malarial disease. This form, therefore, is most commonly observed late in the fever period; in other words, in the months of September and October. The symptom-complex is ordinarily annexed to that previously described for typhoid pernicious, and may last several days and then gradually give way to a long convalescence. If a renewal of the fever occurs during the adynamia, it aggravates the prognosis (Kelsch and Kiener).

In the following we present a case of Kelsch and Kiener's, which shows to what degree of anemia this condition may advance:

B., soldier in the Third Zouaves. Had two years' service in Algeria. Acquired intermittent fever after returning, in August, 1874, from a detachment in the forest, near Jemmapes. The fever, first tertian, then quotidian, finally irregular, resisted treatment; the patient was, therefore, removed on September 27 to the hospital at Philippeville. He left the hospital on October 26 in a very anemic condition after receiving permission to return to France to recuperate. Before going on board, homeward bound, he had, on August 29, a severe attack, beginning with fainting, and from this he fell into a half-comatose condition. This was still continuing when he was brought to the hospital on October 30.

On admission: Stupor; no answers could be gotten to questions. Patient stared vacantly before him, mumbling to himself, and repeating always the same word. The face was expressionless, extremely pale, grayish or somewhat yellowish. The spleen was enlarged. Quinin sulphate, 1.0.

October 31: Stupor less marked, yet continued severe adynamia. During the night, involuntary passage of urine. Temperature, 38.2°. Blood examination: Erythrocytes, 1,090,400; leukocytes, 2585. In the microscopic field, a few melaniferous leukocytes.*

November 1: Patient has again fallen into a half-comatose condition; does not answer when spoken to. The look is vacant, the eyes wide open. Occasionally an idiotic laugh. Involuntary urination. No stool. Temperature, morning, 38°; pulse, 100 and weak. Evening, 37.2°; pulse, 84. Blood examination: Erythrocytes, 931,540; leukocytes, 1980; a few pigmented cells.

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* Malarial parasites had not been discovered.

November 2: Patient slept during the night. The sensorium is more active, the patient answering, though slowly. The memory is cloudy; the expression of the face is that of a lost, feeble-minded character. The tongue is pale and moist. No stool; involuntary urination. Temperature, morning, 35.8°; pulse, 84; evening, 36°. Blood examination: Erythrocytes, 779,260; leukocytes, 3290; no pigment found.

November 3: Remarkable improvement; the memory has returned, and the patient is able to give information as to the beginning of the disease. Voluntary urination; the urine concentrated, but contains no albumin. Weakness marked, color of the face cachectic, continued hypothermia. Blood examination: Erythrocytes, 668,714; leukocytes, 2820; no pigment.

The following days gradual improvement. Patient gained constantly in strength. The temperature varied between 35.6° and 38.8°.

From November 8 the blood-finding improved: Erythrocytes, 1,022,438; leukocytes, 2350; here and there a melaniferous cell.

November 13: Blood examination: Erythrocytes, 1,610,502; leukocytes, 3055. Slow convalescence.

As already mentioned, Kelsch and Kiener had in the adynamic forms a mortality of 25 per cent.

Death takes place in the hypothermic collapse, with an outbreak of sweating, in a faint with coma, or in convulsions.

Convalescence is usually protracted and tedious. The edema of the legs may continue a long time as a result of the anemia and heart weakness. Moreover, thromboses and gangrene are sometimes seen.

CEREBRAL AND SPINAL PERNICIOUS FEVERS.

In addition to the fevers of typhoid character, there are others showing a participation of the brain. These constitute the majority of pernicious fevers in severe malarial regions.

The symptoms which occur in these cases are the same as occur in diseases of the brain generally. In some cases the symptom-complex can be differentiated; in others it simulates exactly an actual organic disease of the brain, most commonly, meningitis. As a rule, the disease-picture is limited to one symptom, or this at least predominates from the beginning to the end.

The pernicious cerebral fevers constitute the principal contingent of Torti's comitatæ, and there are writers who even to-day speak of comitatæ cerebrales. Against this appellation we have nothing to say. Centuries of use have given it a citizen's privilege in medicine. Still we must remember that the cerebral disturbances are not always only culminating, but may occur, too, during typhoid pernicious (Torti's solitariæ), when the comitatæ, in Torti's sense, would not exist.

Among the general brain symptoms we may mention as common headache, vomiting, delirium, stupor, coma, convulsions, and incontinence. Among the local symptoms, hemiplegia, monoplegia, aphasia, and contractures of different groups of muscles.

On the part of the spinal cord (possibly, too, proceeding from the brain), tetanic convulsions.

We will detail the more frequently occurring pictures and illustrate them with examples, paying especial attention to the variable grouping of the symptoms.

COMATOSE PERNICIOUS.

This form is decidedly the most frequent of all cerebral pernicious fevers. Its characteristic stamp is the coma. Naturally, gradations occur, and in isolated cases the disturbances of the sensorium may progress only to deep stupor, though these cases will be described as soporose pernicious.

The coma may come on suddenly, or be preceded by slight disturbances of the sensorium, like somnolence, psychic depression, apathy, melancholia, etc. Moreover, the coma may occur with the first fever paroxysm, or, as is more frequent, several paroxysms pass uncomplicated before it suddenly appears.

The coma may intermit—that is, begin with the rise in temperature, cease with its fall, and thus repeat itself. In these cases it is usually relatively short and seldom exceeds twelve to twenty-four hours. In other cases—and these are the more frequent—the coma continues, with only occasional intervals of slight improvement, until death or recovery ensues. It may then extend over three or four days. It is not rare to see coma in the course of other varieties of pernicious fevers—for instance, typhoid pernicious or adynamic forms. It is associated with no definite type of fever. It may develop during an intermittent, quotidian, or tertian, as well as during a subcontinued.

The face is sometimes flushed, again pale or of a lead color; the latter is especially the case when the patient has become markedly anemic from repeated malarial infection.

The loudest summons calls forth no response or only an unintelligible mumbling. The swallowing reflexes are often abolished, or there is a cramp of the throat, so that neither nourishment nor medicine can be introduced per os.

The eyes are sometimes open, again shut; the balls frequently turned upward. The pupils are usually dilated, but may be contracted, and ordinarily react to light, even though sluggishly. The corneal reflex is commonly preserved.

The pulse is hastened, seldom slowed, sometimes full and compressible, again small and hard. It is usually regular; the opposite is significant of the approaching end (Dutroulau).

The breathing may vary in the same way, being sometimes hastened, again of ordinary frequency; it is often slowed and snorting. Irregularities in the respiration are frequent; occasionally Cheyne-Stokes' type occurs.

The skin is usually warm, and toward the end of the paroxysm bathed in excessive sweat. Not rarely isolated petechiæ are seen.

The limbs are, as a rule, completely relaxed. When lifted up, they fall back lifeless; yet not rarely they manifest, either now and then or throughout the whole paroxysm, irritative motor symptoms like extensor contractures or twitching of the extremities. To these may be added trismus, cramps of the muscles of deglutition, and deviation of the eyeballs.

The skin-reflexes are markedly diminished, yet seldom abolished; some reflexes may be preserved while others are absent. The tendon reflexes are ordinarily intact. Evacuation of the bladder and bowels is involuntary; retention of urine is frequent.

The examination of the internal organs shows, besides the splenic tumor and the occasional increase of heart dulness, nothing abnormal. When certain symptoms on the part of the nervous system—paralysis, contractures, etc.—become prominent, we add the names corresponding to these symptoms—for instance, tetanic or hydrophobic, comatose pernicious (further details later).

With the cessation of the fever the coma disappears under profuse sweating. The patient may come gradually or at once to his full senses. Sometimes there exists for several days a condition of stupor, or apathy with somnolence, even when the temperature continues normal. With a renewal of the paroxysm the coma may recur.

When death occurs, it is usually under symptoms of cardiac insufficiency or paralysis. Edema of the lungs develops, a cold sweat breaks out, the pulse becomes smaller and smaller. The termination is usually quite rapid and frequently unexpected. The temperature remains high, *usque ad finem*, and sometimes *subfinem vitæ* rises to a hyperpyretic degree.

The blood from the peripheral vessels contains, especially as long as quinin is not administered, large numbers of parasites of the second group.* They occur sometimes in one single generation, when the fever is intermittent, or they manifest every stage of development, when the fever is usually subcontinuous. The latter is the more frequent. If quinin has been administered in sufficient doses, the number of parasites, as a rule, diminishes, yet in spite of this the severe clinical symptoms may continue, especially in cases in which the capillaries of the brain are filled with parasites, or in which nutritive disturbances of the brain substance or hemorrhages have occurred.

The **diagnosis** of comatose pernicious comes into question almost only in regions where severe malaria is endemic, yet it occasionally happens that persons who have been infected in severe malarial places depart from these and become ill elsewhere. The possibility, then, of malarial disease must be taken into consideration, even in places free from malaria, when the patient is known to have left a malarial region but a short time before.

A confusion of comatose pernicious with different diseases of the brain and with toxemias is naturally very easy, especially when the anamnesis is not complete. As a matter of fact, such errors in diagnosis are very frequent in malarial regions, where the physicians are inclined to perceive malaria behind most infections. It is usually cases of tuberculous meningitis, cerebral hemorrhage, or softening and uremia that come into question.

Reversely, it occasionally happens in places free from malaria that a pernicious coma does not arouse the slightest suspicion of malaria, and a corresponding error in diagnosis is made.

In addition to the enumerated anatomic diseases of the brain, sunstroke (insolatio) must be taken into consideration. This shows clinically considerable resemblance to comatose pernicious, and a further relation in another way, in that the effect of the sun's rays may produce an outbreak of comatose pernicious in people infected with malaria.

It would carry us too far to go into the differential diagnosis of these different diseases, and I omit it all the more readily since we possess in the blood examination the best means of diagnosing or excluding malaria. In comatose pernicious, especially so long as no quinin has been administered, we constantly find, even in the peripheral blood, large numbers of parasites and melaniferous leukocytes. If the blood-finding is negative and there are, in spite of it, good grounds for suspicion, puncture of the spleen is justifiable. If the case is malaria, this must necessarily be positive.

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* So far only two cases of comatose malaria have been observed, in which the blood showed the ordinary tertian parasites (French, Ziemann).

The **prognosis** in comatose pernicious is always very grave. Even after energetic treatment with quinin the mortality is large. Moreover, cases that show from the beginning a mild form may succumb in spite of the early administration of specific therapy. Even when the coma has passed, the prognosis must remain doubtful, since a second paroxysm may bring with it a recurrence of the coma.

A decrease in the number of parasites in the peripheral blood is in general a favorable prognostic sign, yet it sometimes happens that very few parasites are found in the peripheral blood, at a time when the cerebral vessels are packed with them. Again, the parasites may be absolutely eradicated by the quinin, yet the coma continue and lead to a fatal termination on account of cerebral disturbances of nutrition produced by the toxin of the parasites, or on account of anatomic changes (capillary hemorrhages) caused by the occlusion of vessels.

It is wise, therefore, even when the symptoms are yielding, to be guarded in the prognosis. Nor should we omit to take into consideration all the clinical symptoms, together with the blood-picture in the prognostic calculation.

DELIRIUM.

This is frequently encountered in mild form in fevers both of the first and second group. Yet it sometimes happens that the psychic disturbance is so marked as even to dominate the picture. The delirium may continue throughout a paroxysm or occur only as an introduction to coma.

Kelsch and Kiener divide it into three forms: The first is characterized by violent symptoms, loud cries, maledictions, laughing, and raging. In this form the eyes are injected, stand out; the skin is burning hot. In all these cases they found either insolation or pneumonia as a complication. The second form expresses itself in a fixed idea that is usually gloomy. The patient is in a condition of deep mental depression and endeavors to run away, to throw himself from a window, etc. The third form is characterized by delusions and hallucinations, among which ideas of grandeur, religious notions, and delusions of persecution predominate. The patient may be quiet, distrustful, gloomy, or maniacal. The fever is relatively insignificant. This form continues the longest. Kelsch and Kiener observed one case in which the delirium continued about a week after the paroxysm.

Pasmanik, who saw a very large number of cases, never observed actual mania, but always conditions of depression, usually in the form of melancholia agitata or melancholia simplex.

Since Kelsch and Kiener noticed in their cases with maniacal symptoms the previously mentioned complications, we may conclude with Pasmanik that when malaria does act on the psychic functions, it acts almost without exception depressingly. As an example I introduce a case of Kelsch and Kiener's:

Perez, aged twenty-six, has lived at La Calle (Algeria) one year; breaks stone on the streets of Bona.

Admitted to the hospital December 15, 1874. He contracted fever for the first time three months before, and from September 21 to 27 was under hospital treatment.

Since then he has had several paroxysms, following one another irregularly. During the last fourteen days these have increased in frequency.

On admission no fever and nothing striking in his mental condition. He came on foot. Skin yellow; spleen enlarged.

December 16: During the day a violent paroxysm (40.5° C.—104.9° F.), unaccompanied by a chill. At the evening visit the expression of his face lively, the lips trembling. The patient was talkative and begged that he be cured. He spoke of his misery, while tears coursed down his cheeks. A few moments later he rose suddenly and sprang to the window in order to leave the hospital. Toward evening he became quiet, yet during the whole night he was troubled with dreams and visions.

December 17: The temperature fell under a copious sweat: morning, 38° C. (100.4° F.); evening, 37.2° C. (99° F.). His mind is clear; he is conscious of the mental disturbance that he manifested yesterday. Great prostration, sadness, slow intellection. He denies the misuse of alcohol, in that he refers to his poverty and his sobriety. He assures us that he has had no mental disease.

December 18: Temperature, morning, 38° C. (100.4° F.); evening, 37.3° C. (99.1° F.). Like the preceding, this night was disturbed by visions. He saw the Holy Ghost, found himself transported home, saw his relatives at his bedside. In the morning, gloomy thoughts, wished to die, spoke but little.

December 19: Temperature movement slight: morning, 38° C. (100.4° F.); evening, 36.8° C. (98.2° F.). The same mental condition as yesterday. From this day on, hypothermia.

December 28: The patient wishes to leave the hospital. Although his answers and behavior are reasonable, his mental condition is not normal. His thoughts are full of visions. He thinks he sees a carriage carrying him away. He is sad and reserved.

The anemia and leaden hue are more pronounced than on entrance.

MOTOR IRRITATIVE SYMPTOMS (CONVULSIONS).

Irritative symptoms of slight intensity and well localized are not uncommon during the comatose attack. We mentioned before that trismus and deviation of the eyes were often observed. It happens quite as frequently that the extremities show, either singly or altogether, a transitory slight rigidity, or even a few clonic twitchings.

Rarely these motor irritative symptoms are so marked as to dominate the disease-picture.

Under these circumstances conditions arise which recall epilepsy, hysteria, uremia, and tetanus.

Epileptic convulsions (epileptic pernicious) as a direct expression of malarial infection occur very rarely. They are seen most frequently in small children, who seem to manifest a general tendency to replace the initial chill of various infections by eclamptic convulsions. The infantile eclamptic convulsions, therefore, are not so difficult to understand. When they occur, though in an adult, we should first think of the possibility of the patient being an epileptic or hysteric in whom the convulsion was provoked by the malarial paroxysm. Marchiafava and Bignami observed such a convulsion in a malarial patient. On examination of the blood showing parasites of the first group, they came to the conclusion that it was a case of malaria in an epileptic individual. When the patient awoke from the post-epileptic stupor, he assured them that he had suffered from convulsions for a long time.

Yet the epileptiform seizures may take place in adults, due to the localization of malarial parasites in the vessels of the brain. The following, from Laveran, may serve as an illustration:

A patient with quotidian intermittent was admitted to the hospital in Daya (Algeria). The day after entrance (9 A. M.) he was unconscious, had general convulsions, subnormal temperature, and was pulseless. Recovery after the application of artificial heat. On the evening visit slight stupor, tongue red and dry, skin warm, pulse hard and frequent. 1 gm. quinin sulphate.

The next day a new paroxysm. "I had scarcely moved away from the bed," writes Laveran, "when a cry from the patient brought me back. I found him cold, pulseless, shaken by general convulsions, during which urine and feces were passed involuntarily. In vain I employed excitants; in a few minutes D. was a corpse.

Abelin observed, in Gabun, a pernicious case with two epileptic attacks in the course of one day. Recovery followed quinin.

Several cases of tetanic pernicious are to be found in the literature, though in a well-developed form it is at most a rarity (see Perinelle's thesis).

We take the following case from Marchiafava and Bignami:

M. F., aged twenty, had malaria last year; no manifestation this year until July 30, when he had a paroxysm.

July 31: In the morning he went on foot to his working-place. About midday he was found in a comatose condition by a cousin and was transported by him to the hospital; a physician on the spot had administered, in the mean while, an injection of quinin.

Admitted to hospital 6 P. M.: Patient in deep coma. Trismus (it was impossible even by great force to open the mouth). The arms contracted, the forearms extended pronated, the hands and fingers flexed. The tetanic contractions subsided occasionally to recur unexpectedly. Compression of the vessels and nerves of the extremities called forth no paroxysm during the relaxation. No opisthotonos. The lower extremities contracted in extension, the feet in plantar flexion and slight varus position; the contractions became occasionally less marked, but never ceased.

Abdomen contracted. Respiration of costal type (180 a minute) and rattling. During inspiration the abdomen is drawn in. Pulse 120, soft. Right heart dilated. The eyes turned upward and outward; pupils dilated and react to light.

Now and then paroxysms occur during which the stiffness of the gluteal muscles increases and the pelvis is elevated. The penis in half erection. The patellar reflexes increased; skin reflex normal.

Temperature, 8.30 P. M., 39.7° C. (103.5° F.)—3.0 quinin bimuriat.; 9.00 P. M., 38.3° C. (101° F.) (after cold pack); 12.00 M., 39.8° C. (103.6° F.); August 1, 2.00 A. M., 40° C. (104° F.); 2.30 A. M., exitus.

The blood examination of July 31, 6 P. M., showed only a few endoglobular organisms with central pigment and a few melaniferous leukocytes.

*Autopsy.**—Dura mater tense; meninges very hyperemic; the central gray matter very melanotic; no hemorrhages. Spleen quite soft, melanotic; the Malpighian bodies non-pigmented and conspicuous. Liver soft; slight melanosis.

Microscopically the brain capillaries were found filled with erythrocytes, every one of which contained a parasite with concentrated pigment. Few of these parasites free. The blood taken from a cerebral artery and vein contained only a few parasites.

There was in this case one single generation of quotidian parasites. It is worth remarking that after a mild attack the day previously the second attack led to a fatal termination under the severest pernicious symptoms.

Motor irritation may manifest itself also in the form of a tremor. Sometimes both forms of motor excitement go hand in hand—as, for instance, Schellong's case,† in which rigidity of the neck and of the upper extremities was observed in association with tremor of the head and arm.

PARALYSIS.

Paralyses are much rarer than the motor irritative symptoms, yet a number have been observed, and they are consequently of pathologic diagnostic interest.

These paralyses must, on clinical and etiologic grounds, be divided into groups, depending on whether they occur with the paroxysm, or substitute it, or appear first after it has passed; depending further on whether they disappear with the paroxysm or continue a longer or shorter time after it.

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* Here given in abstract.

† *Loc. cit.*, case history No. 22.

We will discuss especially the paralyses which come and go with the paroxysms, and classify those that substitute the paroxysms with the latent forms; those that continue after the paroxysms, with the complications and sequelæ.

The most frequent form of malarial paralysis is hemiplegia, and, according to Landouzy, this is ordinarily associated with aphasia; among 12 malaria hemiplegia cases which he collected from the literature, 8 were associated with aphasia. Monoplegias and paralysis of individual cerebral nerves are less common.

The paralysis usually occurs during coma, but may develop while the cerebrum is active. On account of the small number of these cases it is impossible to name any type of fever as predominating. It may be quotidian, tertian, or subcontinued.

There are a few cases reported, and these are the most interesting ones, in which the paralysis appeared and disappeared with repeated paroxysms, in which there was, therefore, an actual intermittent paralysis.

The diagnosis of malarial paralysis depends on the proper appreciation of the accompanying symptoms, as the chill, fever, splenic tumor, etc., though the positive result of a blood examination is the only absolute criterion.

It must not be forgotten that in predisposed persons hysterical paralysis, as well as hystero-epileptic attacks, may occur with the malarial paroxysm. In such cases the anamnesis is of importance. The following cases may serve as examples of malarial paralysis:

Boisseau observed in Val de Grâce a man who became infected in Cochin China. During the paroxysm he manifested cephalalgia and a pure motor aphasia without any other paralysis. This lasted seven hours and then completely disappeared. Consciousness was preserved throughout. Altogether the patient had three such attacks (type not mentioned).

Macario observed a woman who manifested, on four successive days, in addition to the fever, the following condition: Horripilation over the entire body, followed by paralysis of all the body muscles, even to difficult movements of the tongue. Speech became almost unintelligible, swallowing difficult, and, in addition, there was paralysis of sensation. No headache. The attack lasted three hours. Recovery followed the administration of quinin.

Marchiafava and Bignami describe the following case:

B. V. has been suffering from fever for two days. Three days before his admission to the hospital he walked and talked well. He was brought to the hospital in a very low condition and received at once injections of quinin (August 29, 1890).

August 29: Morning: Quite prostrated; stuporous; speaks slowly and scanningly; answers questions in a tired sort of way; pretty evident facial paralysis on the left; the tongue is deviated to the left; the pupils are equal; muscle strength of both sides the same; no disturbance of sensation; superficial and deep reflexes normal; bladder full. In the blood a few non-pigmented parasites, many pigmented macrophages. Injection of 1.50 quinin bimuriate.

August 30: Morning visit: Dysarthria; deviation of the tongue continues; some stupor; bladder full (catheterized); temperature subfebrile.

Blood examination (10 A. M.): A very few parasites with pigment-granules and leukocytes with pigment-clumps. In the urine a slight amount of albumin.

August 31: Facial paralysis. Deviation of the tongue, continued dysarthria. The voice has a nasal tone. Paralysis of the soft palate. The patient staggers in walking. During the night involuntary urination. In the blood only melaniferous leukocytes. Apyretic.

September 1: Again fever (38.6°). Injection of 1.0 quinin bimuriat. In the blood a few melaniferous leukocytes.

September 2: After another fever paroxysm which occurred during the night the bulbar symptoms became worse. Secessus involuntarii. Expression of face stupid. In the blood only pigmented leukocytes.

After further injections with quinin, rapid improvement. The nervous symptoms are gradually disappearing, yet there are some remains of the dysarthria in the form of a suggestion of scanning speech.

September 20: Exit.

The prognosis of malarial paralysis is generally good, since it usually passes with the paroxysm. Yet the character of the paralysis cannot be recognized from the beginning. A paralysis the result of hemorrhage may occur during an attack of malaria and produce the same symptoms as one due to a thrombosis by parasites, or to the action of a toxin. The latter may entirely disappear with the paroxysm; the former usually continues a longer or shorter time, and sometimes indefinitely. The prognosis as to the outcome of the paralysis may be forced into the background by the vital prognosis, when the other symptoms are of such a nature that a fatal termination is to be feared.

PERNICIOUS ALGID.

By this we understand a very malignant, frequently fatal expression of malaria, the chief symptom of which consists in an extraordinary cooling of the surface of the body during the hot stage. This is very probably the result of a vascular paralysis in the internal organs, producing a threatening diminution of blood-pressure and a stasis that proclaims itself in the form of a general cyanosis.

The disease-picture is as follows: During the hot stage, in fact, usually at its beginning,* the arterial tension sinks unexpectedly; the pulse becomes easily compressible and eventually disappears. The eyes are sunken and surrounded by a black ring; the pupils dilated. The face is wrinkled and presents a Hippocratic expression. The sensorium is unaffected. The lips are cyanotic; likewise the tongue, which also becomes cold. The surface of the skin is unpleasantly cool; in fact, feels like marble, and is covered with a cold sweat. The pulse is increased in frequency; the breathing is superficial and hastened. The rectal temperature is usually elevated; the axillary, about 38°.

The subjective complaints of the patient are limited, as a rule, to a feeling of extreme fatigue in all the limbs, though he sometimes also complains of a burning internal heat. It is remarkable that the patients do not feel the coldness of the body surface. They never complain of cold, and differentiate the algor from the chill. In the latter case the skin-temperature is objectively little or not at all below the normal, yet the patients complain of cold; while in the algid stage the skin is ice cold and the patient complains either not at all or of an internal burning. The patients are usually uninterested and do not suspect the danger hanging over them. The condition may be fatal in a few hours, and may be protracted twelve hours or even longer.

The prognosis is decidedly unfavorable, though some cases of recovery have been reported.

The condition occurs in intermittent as well as subcontinued fevers, though we must add the algor itself never intermits. When it once appears, it terminates either in recovery or death.

The algor is frequently secondary to severe participation of the gastro-intestinal tract (further details later), though it occurs, too, as an independent symptom. In the latter case it is in all probability the result of the action of the toxin on the vasomotor centers. Proceeding from this assumption, we will consider the pure algid form under the cerebral pernicious fevers. Laveran observed the following case of algid pernicious:

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* According to Torti, the algor occurs in the cold stage and is nothing else than its prolongation ". . . cum Frigus quoddam mortiferum incipienti Paroxysmo jungitur quod non, ut assolet in Benignis, paulatim evanescit, ut illud sensim calor excipiat; sed protrahitur, et protrahitur," etc.

B., aged twenty-three, soldier, was brought into the hospital at Constantine, July 27, 1882, 11 P. M. He had been employed as a gardener, and had suffered from fever several times. He appeared at the hospital on July 27, on account of a recurrence which, at the time, showed nothing at all suspicious of perniciousness. The battalion physician ordered 1 gm. quinin sulphate in pills. The same evening his condition became suddenly worse and he was brought at once to the hospital. On admission he was extremely weak, yet in possession of his senses. He sighed deeply from time to time, but when asked how he felt, complained only of weakness and prostration. The extremities were cold, the pulse quite rapid, and impalpable in the radial artery. It was 120 in the carotids. The heart-beat was rapid and feeble; respirations hurried, but deep.

The rump was warm to the feel. The temperature was not taken. Pupils were dilated. Secessus involuntarii urinarum. Subcutaneous injection of 1.50 quinin; frictions, sinapisms, warm drinks. The algor progressed rapidly.

July 28, 3.30 A. M.: The death agony. Half an hour later the end.

The autopsy showed the signs of a severe malaria. In the blood of the organs enormous numbers of parasites were found.

SYNCOPAL PERNICIOUS.

Closely connected with the algid form, though rarer, the syncopal likewise depends on a diminution of blood-pressure. The patient falls into a deep faint on the slightest effort, as, for instance, the act of sitting him up straight, or, as Torti mentions, of turning him from one side to the other, or even a personal attempt on his own part to raise his hand.

These patients also show the subjective and objective symptoms of extreme weakness; the pulse is small, easily compressible, rapid; the forehead and neck are covered with a light sweat.

Torti affirms that the intermission after such a paroxysm may be quite bearable, yet woe to the physician who believes himself in security and omits the necessary medication. The next attack may prove fatal, and the reproach which Hippocrates once made be applicable: "Medicus non intellexit; puella mortua est."

DIAPHORETIC PERNICIOUS.

This belongs also to the group of algid forms. It is characterized by symptoms of collapse, and, in addition, an excessive secretion of sweat, from which it receives its name. The profuse perspiration occurs sometimes at the beginning of the warm stage, and may then give rise to the error that the paroxysm was short; or it may appear at the close of the paroxysm.

Torti, who passed through a severe attack of diaphoretic pernicious fever himself,* describes the condition in the following words:

> "Fraudulentior est ea febris, quæ nullo præcedente pravitatis indicio Aegrum invadit more solito cum horroro, rigore, et frigore cui succedit calor, et statim sudor aliquantulum præcox, qui equidem februm videtur primo aspectu alleviare, sed revera post illum potius intenditur febris, quam remittitur; immo eo fortior videtur fieri, quo copiosior est sudor. At ille not est terminus. occultæ fraudis, hinc enim potius longitudo morbi significatur, quam mors. Quod pejus est, frigefit paulatim sudor, et in diaphoreticum sensim degenerat. Sudat perpetuo ægrotans, et deffluit undequaque frigido sudor perfusus; sicque perpetuo algens, et sudans sicut cera liquatur, dissolvitur et deficit. Pulsus celer est, minutus, ac debilis, respiratio fit anhelesa, et frequens, dissipantur spiritus, et viryus universaliter languet. Mens sola lucidissima est, et sentit homo, se paulatim mori. Nisi autem hoc illa ipsa accessione succedat, in proxime futuram tantum protrahitur" (Lib. iii, Cap. i).

GASTRO-INTESTINAL PERNICIOUS.

After the nervous system, the gastro-intestinal tract is the most frequent seat of severe symptoms in pernicious malaria.

We have already mentioned (p. 262), in describing the general symptoms of pernicious infections, that vomiting, diarrhea, epigastric pain, and icterus were frequent occurrences. When these symptoms become conspicuous, we speak of a bilious remittent fever. This form becomes pernicious only on the occurrence of special complications.

In addition to this form we differentiate, since Torti's time, several others associated with prominent participation of the digestive tract, which become threatening through the occurrence of algid symptoms. These frequently take on the mask of other infectious diseases affecting the intestine.

These gastro-intestinal pernicious fevers are endemic, especially in the tropics, and we owe the majority of our modern descriptions to French or English marine or military physicians, who had the opportunity of studying them in the colonies.

They occur also in southern malarial regions, as Algeria, Italy, etc., but less frequently, and are there usually characterized by less severe symptoms. In past centuries they were more common in these regions, as is proved by Torti's communication, in which they are given considerable space.

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* Lib. iv, Cap. ii.

They played their most important rôle, before the days of accurate microscopic diagnosis, in India, Cochin China, Sénégal, and Madagascar.

The diagnosis was extremely difficult, especially in countries like India, where other intestinal diseases, as cholera and dysentery, are endemic. This difficulty of diagnosis was so great that entire epidemics or endemics sometimes passed without the physician being able to agree whether they were this, that, or the other disease. It is to be hoped that now, with the general spread of the knowledge of malarial parasites, this confusion of the tropical fevers will be rapidly cleared up.

CARDIALGIC PERNICIOUS.

This is characterized by intense epigastric pain ("acerrimus morsus oris ventriculi"—Torti), which comes on during the paroxysm, usually during the hot stage, and ceases with its termination, though it may occur independently of the fever paroxysm (Colin). The pain sometimes radiates to the spinal column, is often accompanied by vomiting, or, if this is absent, by violent choking sensations. The abdomen is usually contracted and extremely sensitive to pressure. The excruciating pain produces intense restlessness, and the patients turn from side to side, groaning and whimpering. Not rarely the patient's condition is made worse by a tormenting singultus. In addition we frequently see, probably as a secondary effect of shock, cyanosis, lipothymia, etc. The life of the patient may be seriously threatened. Conditions deserving the name of "apparent death" are not rare (Daville).

Torti gives the following description of a paroxysm observed by him:

> It occurred in a woman who had suffered repeatedly from tertian fever. With an attack in 1707, the cardialgic symptoms came on. The worst paroxysm ran its course thus: " . . . vehemens siquidem per totum principium, augmentum, atque etiam statum accessionis increbuit Cardialgia, vi cujus ægra sibi erodi, et mordicari a canibus ajebat orificium stomachi. Ejulabat, dum poterat; sed sæpius intercepta voce deficiebat animo: sicque alternatum ululans, suspiria edens profunda, vomitus inanes tentans, et animo deficiens, subfrigida cum minutis circa frontem sudoribus, cum pulsu exili, et crebro, cum facie, semimortuam referente, oculis caligantibus, et temporibus collapsis, animam jam prope reddere videbatur. Quia vero per brevissima intervalla nonnulla identidem prodebat signa reviviscentiæ, pulsusque tunc temporis nonnihil resurgebat . . ." (Lib. iv, Cap. i).

We take the following description from Kelsch and Kiener:

> Grigno, aged fifty-two, day laborer, employed in the cork harvesting. Admitted to La Calle Hospital August 8, 1874. Had his first fever three

months before. At the present time, nine days ill. The disease began with a chill, bilious vomiting, and diarrhea. Since then repeated chills at irregular intervals, continued vomiting, and diarrhea.

Status August 9: Facies Hippocratica. Eyes sunken in, injected; cheeks hollow; mouth open, crusted; hands and face cold; cyanosis; incessant jactitation.

Temperature in the axilla, 39.9°; in the rectum, 40.5°; pulse rapid and very small. Patient complains of a burning in the epigastrium. During the night and morning vomited several times. The abdomen is contracted and is very sensitive to pressure. The spleen is enlarged. No stools since admission.

At 3 o'clock: Algor more developed. The extremities ice cold; temperature, 39.5°; in the rectum, 40.3°. Vomiting has ceased. The first clyster of 1.0 quinin sulph. was at once thrown off; the second was retained. Wet cups to the abdomen. Stimulating drinks.

August 10: Continued restlessness. Excruciating internal burning. Tongue dry and rough. Epigastrium contracted and very painful. No vomiting. Two diarrheic evacuations. During the night a profuse sweat. Algor and cyanosis somewhat less than yesterday. Temperature, 37.2°; in the rectum, 39.2°. In the blood, melaniferous leukocytes.

3 o'clock: Restlessness less marked. Dry friction and six leeches to the epigastrium caused a diminution of the sensation of internal burning. The nose, forehead, and hands cool; the rest of the body warm. Temperature, 39°; in the rectum, 41.1°.

August 11: Decided improvement. The fever is lower and the distribution of the surface temperature more natural. Temperature in the morning, 38°; evening, 37.4°; in the rectum, 38.6° and 37.9° on each occasion. Restlessness less marked; epigastric pain quieter; tongue still dry; the voice weak; the extremities cool and somewhat cyanotic. No vomiting. One diarrheic stool. The abdomen still contracted, but less painful. Pulse, 92. The urine cloudy, reddish, and larger in amount than on the preceding days, measuring 900 c.c.

August 12: Same condition, with slight improvement. Morning temperature in axilla, 37.2°; in rectum, 37.3°. Evening, 37.4° and 37.3°.

August 13: Apyrexia. Strength not yet returned; the tongue still dry.

Later a left-sided pneumonia developed, to which the patient succumbed.

Kelsch and Kiener insist that the excessive employment of emetics and cathartics may produce the cardialgia. Colin considers the so-called gastralgic, emetic, dyspneic, pleuritic, pernicious cases as subforms of the cardialgic, which differ from it only in the location of the pain.

CHOLERAIC PERNICIOUS.

This is the most common form of pernicious malaria associated with gastro-intestinal symptoms. In tropical as well as subtropical regions it is exceedingly frequent; in the malarial regions of the temperate zone, at least in our day, it follows in frequency the cerebral forms. It is especially this form that leads to errors in diagnosis in tropical countries, in that it imitates the picture of cholera morbus. This syndrome occurs so frequently that we are scarcely surprised to find an investigator like Fayrer come to the conclusion that cholera, dysentery, and malaria are closely associated etiologically.* Davidson also insists that the relations between cholera and malaria are too manifest to be questioned, though these are of such a complicated nature that they cannot be reduced to any definite rule.†

The situation is further complicated by the fact that malaria and cholera are frequently endemic in the same place, on account of which choleraic pernicious is readily mistaken for true cholera, in the same way as a case of arsenic poisoning may pass unrecognized during a cholera epidemic.

In order to show the importance of this question in India the following passage is quoted from Sir Joseph Fayrer's work: ‡

> "Ancient Hindu authors, observes Mr. Andochurn Kastogiri, a learned Bengali physician and graduate of Calcutta, mention symptoms of cholera as being prominent in a certain type of fever called jewaratishar, literally, 'fever with excessive diarrhea,' and he remarks: 'It has been observed that both may break out simultaneously, or one follow in the track of the other. In practice mixed attacks of cholera and fever are frequently seen.' An attack beginning with symptoms of fever may end with cholera, or vice versâ. And even recently such an epidemic was devastating Amritsar in the Panjab. A report says: 'Choleraic fever is still raging in Amritsar. Business is at a standstill, and nine-tenths of the shops have been closed. A correspondent describes the appearance of the place as a city of the dead. He adds that not a single European has escaped an attack, and that the railway, post, and telegraph officers are working under great difficulties, owing to sickness among the employees.'
>
> "A telegram from Lahore, dated October 4, ran thus: 'Two thousand, two hundred and sixty-five persons died at Amritsar during the eleven days ending with the first inst. One-half of these were children. The heavy mortality is almost wholly owing to choleraic fever, which still prevails in many towns in the Panjab. Considering that the Amritsar medical and municipal staff is greatly overworked, and that natives are always reluctant to give information of deaths, the foregoing figures must be below the mark.'
>
> "The fever here referred to is described to me by the medical officers who witnessed it,—Dr. Duke, of Amritsar, and Dr. Ross, now of Delhi,—who have sent me the following information:
>
> "Dr. Duke says: 'Since my arrival here on November 9, 1881, the fever has offered no special aspect; it has not been of a choleraic type.

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* *Loc. cit.*, p. 60.

† *Loc. cit.*, p. 148. It is not evident from the text whether Davidson meant that both diseases had a common etiology, or that only certain external conditions (telluric, meteorologic) were common to both.

‡ *Loc. cit.*, p. 61.

The symptoms have been those of malarial fever. Our hospital medical wards are filled with pale, anemic men, with dropsy, enlarged spleen, diarrhea, and dysentery, supervening on fever and starvation; for, as the Kashmeeris were attacked with fever, their looms were stopped, and they earned no food. Neither typhus nor typhoid has been observed, nor have any cases of fever with a rash been observed in the city. The death-rate has fallen to 50 per 1000, only 10 or 15 per 1000 above the usual state of Amristar, which has 150,000 inhabitants. I will send you notes on any cases of typhoid or other special fever that may hereafter come under my notice.'

"Dr. Ross says: 'My opinion is that the fever was a special type, which appears in cholera years, and resembles relapsing fever very closely. The course and progress of the disease were distinct from ordinary malarious fevers, and neither typhus nor typhoid existed. Some 12,000 people died in two months or thereabouts; the fever that existed in the jail and civil stations was quite distinct. I send extracts from notes I sent to the Surgeon-General bearing on the epidemic, but have no records of cases.

" 'The rainfall here in 1881 is reported to have been rather more than twice the average fall of the last fifteen years. It fell principally over the city and around the outskirts of the city. Average rainfall at Amritsar during the past fifteen years was 24.9 inches; the rainfall of 1881 was 52.2. At Tarantaran, a station 15 miles from Amritsar, 68.5 were registered, this being the maximum rainfall.

" 'The heavy rainfall, which commenced in June, caused immense collections of water over a tract of canal-irrigated ground to the north and northeast of the city of Amritsar; the two natural drainage channels, the Gumtala Nulla and the city ditch, being quite inadequate to carry off the water. The consequence was that the water-level rose to an unprecedented height, bubbling up like miniature geysers; all the wells became thoroughly polluted, and the water tasted distinctly brackish.

" 'Fever in the city did not appear in an epidemic form until September; it was preceded by cholera about the beginning of August, of an extremely fatal type, and, later on, when masked by fever, there was some difficulty in recognizing it in time.

" 'The fever, which prevailed with its utmost force in September and the early part of October, appeared to be of the relapsing fever species, but with some affinity to cholera. There were the rigors, fearfully severe, headache, insomnia, disordered bowels (often constipated), fever, suppression of urine, with death from coma frequently within a few hours after seizure, but then the rice-water evacuations and vomit of cholera appeared in very many instances during the course of an attack of the fever.

" 'The two diseases, cholera and fever, supposing them to be distinct, certainly masked one another so effectually that diagnosis was extremely difficult at times. The people, by the end of October, began to show the exhausting effects of the epidemic fever: enlarged spleen, anemia, debility, jaundice, and the usual sequelæ told fatally on their enfeebled constitutions.

" 'This specific fever was strictly confined to the city and to those only who had to go inside on duty.' "

After reading this account there is no doubt in my mind that this was an epidemic of choleraic pernicious, for Dr. Ross' description of the sequelæ (dropsy, anemia, splenic tumor, etc.), as well as that of Dr. Duke, who arrived only after the principal epidemic, is very evidently one of malarial cachexia. Whether true cholera existed at the beginning of August, before the choleraic pernicious, as Dr. Ross believes, cannot be judged, on account of the shortness of the report.

Choleraic pernicious is by no means limited to the tropics. Siredey, for instance, reports six such cases, one of which ended fatally in Montaut (Basses-Pyrénées) in 1884.

The chief symptoms of choleraic pernicious fever are profuse diarrhea and vomiting.

The stools are in the beginning somewhat yellowish, later serous, and sometimes slightly sanguineous, and finally clouded by small mucous flakes, desquamated epithelium, etc., giving them the character of rice-water stools. Not uncommonly there is pain in the epigastrium or abdomen generally.

When the condition continues, algid symptoms appear, as coolness of the skin, cyanosis, cramps in the calves of the legs, thread-like pulse, etc., so that the picture simulates more and more the algid stage of cholera.

As a differential diagnostic point between them Torti mentions the fever. He writes: "Uno verbo, omnia accidentia, quæ Choleram morbum comitarti solent, a quo tamen distinguenda est hæc affectio quasi cholerica, inquantum est merum symptoma febris supra consuetam intensionem adauctum, et febris ipsius periodum, ac motum subsequens, velut umbra corpus."

When the patient had previously one or more paroxysms of fever and the temperature in the rectum is found elevated, the diagnosis, even apart from the blood examination, is easy. If the attack begins with a chill, the diagnosis is evident at once; in the rarer cases that begin with vomiting and diarrhea and rapidly show algid symptoms, with eventually death, confusion with cholera morbus is difficult to avoid.

When the clinical symptoms leave in doubt, the blood examination becomes the only means of a positive diagnosis. So far there have been but few cases of choleraic pernicious in which a blood examination was made, yet the following one, from Marchiafava and Bignami, shows that even here numerous parasites may be found in the peripheral blood. It is to be hoped that the future will gather more information.

A mixed infection of malaria and cholera can be proved only by the simultaneous finding of malarial parasites and cholera vibrios. As far as I know, no such case has as yet been reported.

According to Kelsch and Kiener, the algid symptoms seldom last longer than twelve hours, and from their experience, the prognosis is not extremely serious. Still the condition shows striking variations in different localities and individuals.

Marchiafava and Bignami describe the following case:

C. G., aged fifty-four, a cook from Porta S. Giovanni (Capannello), was brought in a wagon to the hospital on September 5, 1890, at 2 P. M., accompanied by a watchman. The disease began on September 2. The patient was in a condition of anxious excitement, and became delirious when left to himself. Facial expression anxious; pupils dilated; skin cold and covered with a viscid sweat; cyanosis of the lips and extremities; pulse frequent and thready; spleen slightly enlarged. He had a profuse diarrhea, and in the morning vomited, even on the street. In the hospital he manifested a cholera-like diarrhea and nausea. The blood examination showed numerous non-pigmented ameboid parasites. He was given 2.0 quinin by injection and the same by the mouth. Friction, injection of ether, camphor, etc.

8 P. M.: Profuse sweat. Skin still cool; delirium has ceased, and is replaced by continuous lamentations. Pulse small and rapid. Diarrhea continues.

During the night the diarrhea lessened, the skin became warmer, and he had several hours' rest.

September 6: Morning, considerable improvement. Pulse, 90, strong; the algor has passed; temperature, 36.6°. The cyanosis has disappeared. Still a few diarrheic evacuations. Quinin, 2.0; cardiac stimulants and wine. In the blood only a few ameboid, non-pigmented parasites.

6 P. M.: Apyretic. Pulse strong; diarrhea has ceased; pallor and prostration continue. Quinin, 1.0.

During the following days progressive improvement. Strength returned gradually; appetite increased; the parasites disappeared from the blood and there was no further fever.

DYSENTERIC PERNICIOUS.

In this form the fever paroxysm is accompanied by bloody and mucous stools and tenesmus. There are abdominal pain, stomachache, and, in one word, all the symptoms ordinarily seen in dysentery. Algor is rare, and the prognosis is, therefore, more favorable than in choleraic pernicious forms.

Some observers of experience (for instance, Colin) deny that the symptoms of dysentery can be produced by malaria alone, and claim a mixed infection in these cases. This is a problem for parasitology. We have preserved dysenteric pernicious on account of a series of publications which would otherwise be valueless.

Torti differentiates still another form that may come in here, namely, *subcruent* or *atrabilious pernicious* (sanguineous or black bilious pernicious).

This is characterized by profuse diarrhea, first yellowish and serous, later sanguineous, following which algid symptoms appear. The blood is intimately mixed with the stools and may be either fluid or coagulated. It must, therefore, come from the upper part of the intestine. This form is differentiated from the choleraic by the absence of vomiting and the bloody stools; from the dysenteric, by the absence of tenesmus and the inclination to algor.

Recent writers have bestowed no further attention on this symptom-complex,* though Torti's precise description leaves no doubt as to its occurrence.

BILIOUS PERNICIOUS.

(Syn., Biliaris Remittens; Fièvre Pernicieuse Bilieuse; Grande Endémique des Pays-chauds; Remittent Fever; Bilious Inflammatory Remittent Fever; Jungle Fever, etc.)

The most common summer and autumn fevers in some malarial regions (the coasts of the Mediterranean Sea, Africa, Madagascar, India, etc.) are those associated with more or less pronounced icterus and gastric disturbances. As mentioned on page 262, these frequently run a favorable course, though often, too, they manifest acutely dangerous symptoms, which, if recovery takes place, may leave behind lasting chronic disease. It is these severe cases which we intend to discuss here.

Natives and the acclimatized, as well as new arrivals, may prove victims. According to some authorities, the not yet acclimatized, especially those who have just arrived in the tropics, are attacked the most frequently.

The disease is usually ushered in with prodromes, which consist in general weakness, pain in the loins and limbs, loss of appetite, and coated tongue. The temperature is, even at this stage, often somewhat elevated.

In other cases a few mild intermittent fever paroxysms may precede, and again the prodromes may be entirely wanting.

The attack itself seldom begins with a chill, and the "first stage" limits itself either to a chilliness or is absent. The patients complain principally of headache, frequently radiating from the eyeball, excruciating pain in the loins and in the limbs, loss of appetite, vomiting, and prostration. The face is usually flushed and turgid; the conjunctivæ are injected, and photophobia is frequent.

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* It is possible that the observation of Frerichs applies to it. See the section on Intestinal Complications.

The type of fever is variable, the malignant tertian type being most common. Less often we see from the beginning short, sharp, intermittent quotidian or ordinary tertian paroxysms. In many cases where the fever began with a remittent type we see later, usually under the influence of quinin treatment, a pure intermittent. Moreover, the reverse is not rare, namely, the appearance of a subcontinued type, after several sharp, intermittent quotidian or tertian paroxysms. The remissions are often only suggested, lasting not more than two or three hours, though in other cases we see intervals of thirty-six hours' duration without a paroxysm.

According to Fayrer, the first paroxysm is usually the longest, while the succeeding ones are more severe and come on without a chill.

The remittent or continued fever may extend over six or seven days, even when quinin is employed, though, as a rule, it goes over into remittent in a shorter time. The sweating stage is only suggested or is absent.

The gastro-intestinal tract manifests the most striking symptoms. These consist in anorexia, epigastric pain, ructus, pyrosis, and vomiting. The epigastric pain is of varying intensity: it is usually pretty severe, sometimes occurs as frightful paroxysms of cardialgia, and rarely is entirely absent. The epigastric sensitiveness is sometimes so great that the patient cannot bear the weight of the bed-clothes.

Vomiting is one of the most constant symptoms. Fluctuating between vomiting and nausea, it is a dreadful torment. The attacks of vomiting are more frequent at the beginning. They often continue day and night. The vomit is greenish from the biliary coloring-matter as long as hydrochloric acid continues in the stomach; later it becomes brownish yellow and finally bloody, coffee-ground-like, as the end approaches.

Constipation is frequent, though profuse diarrhea is not rare, so that from this and the vomiting the suspicion of cholera may arise. The stools, too, contain considerable bile, and are in the beginning dark brown; later, clear yellow. In the very severe cases the stools become bloody antemortem. Singultus frequently occurs as a preagonic symptom.

Icterus is one of the most important symptoms. It is usually seen from the beginning, and even suggested during the prodromal period. In the majority of cases it is limited to the sclera, though it may become very extensive.

As shown in the section on Pathogenesis, this is a polycholic icterus, due to the increased destruction of the red blood-corpuscles. The bilious vomiting and the bile in the stools are also to be included under the polycholic symptoms.

A bronchitis increasing with every paroxysm is frequently seen from the beginning. Delirium, stupor, carphologia, show the participation of the nervous system. Hemorrhages, like epistaxis, hematemesis, are occasionally observed.

Micturition is usually undisturbed, yet sometimes there are strangury and sensations of burning. The amount of urine is variable: with profuse diarrhea and frequent vomiting it is often very slight. The urine is dark in color; it contains urobilin in large amounts; more rarely, in addition, bilirubin. Albumin in considerable quantities is frequent.

The blood shows a rapid impoverishment of erythrocytes. Whether hemoglobinemia exists in these cases has not been investigated; yet the marked destruction of blood-corpuscles and the polycholia make it probable that it does exist at the beginning or before the beginning of the paroxysm.

As a result of the hydremia the patient develops, in the course of the disease, or more commonly during convalescence, an edema that may be general or limited to the ankles.

Under the exhaustion produced by the hemolysis, vomiting, diarrhea, and the impossibility of administering nourishment, the general condition sinks rapidly. The adynamia and algor especially become threatening, and coma is not infrequently added, to which the patient succumbs. Sometimes, especially in Hindus and negroes, pneumonia and bronchitic complications occur to render the condition worse. Symptoms of a hemorrhagic diathesis, in the form of epistaxis, melanemia, hematemesis, petechiæ, etc., favored probably by the hydremia and icterus, may likewise appear.

The duration of the disease, when uninfluenced by quinin, is usually about ten to twelve days (Kelsch and Kiener), though severe cases may be fatal, in spite of quinin treatment, during the first days or in the course of the first week.

The diagnosis presents many difficulties. It is exactly the subcontinued bilious malarial fevers which often show, from a clinical point of view, no sharp separation from other similar diseases occurring in the tropics.

There is no doubt that errors in diagnosis are frequent, especially in India, which appears to be the breeding-place of the different bilious infectious diseases. We need only recall the other forms of infectious icterus, Weil's disease, icterus gravis, acute yellow atrophy of the liver, to realize that the similarity of these conditions with a bilious malaria can be very close.

Fayrer states that confusion with yellow fever is especially likely when, in addition to the icterus, melena and hematemesis occur. Very severe cases of this kind were observed by Evers in Wardha (Nagpur district). They began with violent headache, epistaxis, hematemesis, melena, and high fever, and terminated quickly in icterus, subnormal temperature, coma, and death.

When the fever-curve is not pathognomonic,—and it is this only in the rarest cases,—I believe that a rational diagnosis is assured only by the finding of the parasites. Yet this by no means asserts that the physicians in the tropics before the introduction of the microscope were not in a position to diagnosticate a bilious malaria. Familiarity with the disease-picture obtained by daily observation gives a practical acquaintance that obviates many difficulties. Naturally such diagnoses would not be free from error.

The prognosis is dubious, both when the symptoms are only severe and when actually threatening (diminution of pulse tension). In general, the majority of cases recover on specific treatment. Algor, adynamia, coma, singultus, and anuria are unfavorable symptoms.

Even when the outcome is favorable *quoad vitam*, there remain severe anemia, edema, irritability of the gastro-intestinal tract, and frequently chronic malarial cachexia.

We take the following example of a gastrobilious remittent, associated with albuminuria, and followed by anasarca, from Kelsch and Kiener*:

H., artillery man, aged twenty-five, has been three years in Algeria. Alcoholic. No previous disease. He passed the night between August 9 and 10, 1878, in the open air, exposed to a draft. When he awoke he experienced a pain in the back that prevented him from rising. He was put to bed, and during the course of the day suffered from severe chills and bilious vomiting.

August 11 *and* 12: Continued fever, alternating with cold and hot sensations. Intense headache in the orbital region. Nightmare. After food or drink, vomiting. Admitted to the hospital at Bougie, August 13.

August 13: High fever, flushed face, pronounced weakness, nightmare. Tongue covered with a yellowish coat, nausea, occasionally bilious vomiting, epigastrium sensitive to pressure, two or three yellowish stools. No evident enlargement of the liver or spleen. Urine orange colored, clear, and shows, with nitric acid, a dark-brown ring.

August 15: Fall of temperature without sweating. At 2 P. M.: A paroxysm of fever associated with chilliness.

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* *Loc. cit.*, p. 455.

From this time the fever preserved the quotidian intermittent type, its rises being accompanied by chilly sensations. During the remissions the skin was dry and red. The gastric disturbances improved somewhat; the diarrhea continued, and the urine showed hematin.

August 19: The patient took yesterday 1.20 cinchonidin sulph. The evening paroxysm was less marked. This morning, moderate fever. The flush on the face has disappeared and is replaced by an evident icterus. The urine shows the color of concentrated bouillon, is somewhat cloudy, clears up on heat, and shows, with nitric acid, a mahogany-brown color, even more intense than before.

August 20: Apyrexia. The urine still contains hematin, yet less than previously.

August 21: Urine of normal color, and shows, with nitric acid, a light-brown color. The icterus begins to disappear; the appetite is increasing.

August 30: Edema of the legs, extending to the trunk. The urine contains considerable albumin, and shows again, with nitric acid, a brown color.

September 2: General anasarca.

September 5: Urine copious—three or four liters—and pale. Albuminuria slight. The anasarca is decreasing.

October 1: Patient permitted to depart.

We take the following case of bilious pernicious, associated with adynamia, and ending fatally, from Laveran*:

G., sergeant. Came into the hospital at Constantine (the chief physician, Aron's ward), September 25, 1881. He asserts that he has been ill only four days. His work was at Bardo, a well-known insalubrious locality.

The disease began with anorexia, general malaise, headache, and pain in the limbs. He had no chill and neither recently nor previously outspoken fever.

On September 25, the highest fever. Morning temperature in the axilla, 40°; evening, 39.2°. The scleræ and skin are intensely icteric. The patient answers questions directed to him, yet shows a pronounced inclination to torpor and adynamia. He says that he feels no pain. The tongue is red, dry, and fissured at the tip. Sordes occur on the teeth. The abdomen is yielding and painless. The right iliac region manifests no tenderness on pressure. The spleen is within the margin of the ribs. Pressure on the splenic and gastric region occasions no pain. The liver does not appear enlarged.

Diagnosis.—Febris biliosa malarica. Quin. sulph., 1.5; lemonade, calomel, 1.0, was ordered to be given on the morning of September 25.

September 26: Fever less high than yesterday; temperature: morning, 38.3°; evening, 38.5°. Yet this remission was not accompanied by an improvement in the general condition, but the contrary. The icterus is more marked than yesterday. Stupor and adynamia striking. Pulse, 80.

The voice is faint, husky, like in cholera. Tongue dry, fissured. Constipation. Abdomen painless. Quin. sulph., 1.0.

The patient vomited the quinin, and, in the course of the day, his condition became rapidly worse. Deep adynamia, stupor, bilious vomiting, almost complete aphonia—1.0 quin. sulph. in clyster. Iced drinks, morphin, 0.04 in solution.

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* "Traité des Fièvres Palustres," 1884, p. 130.

September 27: General condition worse. During the night, several times bilious vomiting. Subdelirium. Involuntary stools.

The icterus has again increased. Temperature, morning, 39.6°; evening, 38.6°. Deep adynamia. Mucous membrane of the mouth and throat very dry. Total aphonia, bilious vomiting, involuntary fecal evacuations. A quinin clyster was thrown off. In the morning and evening a subcutaneous injection of 0.60 quinin mur. and 0.01 morph. mur., in order to quiet the vomiting. In the evening, a mustard-plaster to the epigastrium.

During the following night the vomiting continued. Singultus, subdelirium, from which the patient fell into a condition resembling coma.

September 28: Morning temperature, 37.4°; general condition still becoming worse. Pulse very small and rapid. Stupor more marked, adynamia, continued bilious vomiting, singultus. The extremities are cool; the pupils contracted. General hyperesthesia, especially on the skin of the abdomen. Subcutaneously, 1.0 quin. mur. Tea with rum, wine. Evening temperature, 38.9°.

September 29: Condition still worse, though no new symptoms have appeared. Temperature: morning, 38°; evening, 39°.

10 P. M.: *Exitus letalis.*

The autopsy* showed especially a soft, diffluent tumor of the spleen, associated with an intense brown pigmentation; marked enlargement of the liver, associated, too, with brownish pigmentation and diminished consistence. The biliary passages were patulous; the gall-bladder showed considerable dark-green bile. Several areas of lobular pneumonia in the inferior lobes of the lungs.

Microscopically, an enormous number of pigmented organisms were found in the spleen, liver, and bone-marrow; smaller numbers in the capillaries of the brain.

HEMORRHAGIC PERNICIOUS.

Isolated scattered petechiæ, as well as epistaxis, hemorrhages into the posterior chamber of the eye, etc., occur not infrequently in different forms of malaria, especially the bilious.

An acute malaria, associated with marked hemorrhages, simulating the picture of morbus maculosus Werlhofii, or scorbutus, or a combination of both, is rare, though such cases have been undoubtedly observed (Eisenmann, Wenmarning). Marchiafava and Bignami report two cases, one of which† was extremely severe. Tchouprina reported a case of a child with hemorrhages from the nose and gums and numerous petechiæ. The child came from a location where, according to the father, numerous children manifested the same symptoms.

In these cases it is always necessary to examine carefully for a complication of the malaria with one of the blood diseases. These complications should be thought of in poorly nourished individuals living in damp dwellings and poorly constructed caserns, especially when other persons manifest, at the same time, similar hemorrhages without malaria. In campaigns in the tropical regions such mixed infections are often observed in large epidemics. Haspel reported these mixed forms in Algeria, and described them under the name "Fièvre putride, scorbutique, épidémique."

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* Here detailed in abstract.

† *Loc. cit.*, p. 135.

HEMOGLOBINURIC BILIOUS FEVER.

(Syn., Schwarzwasser Fieber; Gallenfieber Fièvre Bilieuse Mélanurique; Fièvre Bilieuse Hémoglobinurique; Fièvre Bilieuse Hématurique; Fièvre Jaune des Créoles ou des Acclimatés; Blackwater Fever.)

Our knowledge of this form of malarial fever is relatively recent, dating back only to the beginning of the fifties. Among Torti's otherwise complete descriptions there is no suggestion of blackwater fever. This is explained by the fact that it is endemic in tropical and subtropical regions, and only exceptionally occurs in higher latitudes, and only then when it is introduced.

The first reports of this peculiar, and in many ways interesting, affection, the genesis of which is not yet fully understood, came from French naval physicians, who observed it at Mayotte and Nossi Bé (Lebeau Daullé, Le Roi de Méricourt). It was likewise physicians of the French marine who showed its occurrence on the west coast of Africa and in America (French Guiana, the Antilles), and gave a complete description of the clinical picture (Dutrouleau, l'Herminier, Barthélemy-Benôit, Bérenger-Féraud, Pellarin, Corre, O'Neill, and others).

The chief seat of blackwater fever is the west and east coasts of Africa. [It extends along the west coast of Africa to Nigeria, Kamerun, the Kongo, Portuguese West Africa, but whether further south than Damara Land is uncertain. It is commonly met with in British Central Africa, British East Africa, Uganda, German East Africa, and south as far as Delagoa Bay, if not further. In Madagascar, Mauritius, Bourbon, and the Comoro Islands it is also known. In the Sudan cases are now being reported from the district of Bahr-el-Ghazal, and on the western side as far north as Kayes. It occurs also in Algeria, but not commonly.—Ed.] [It occurs also in Java, Sumatra, and New Guinea, and in parts of Cochin China and Tongking. In America it occurs in most of the Southern States, in French, Dutch, and British Guiana, in Central America, Nicaragua, Costa Rica, Venezuela, and in Cuba, and also probably not uncommonly in Brazil. In the European fever countries it is seen in southern Italy and Greece, Sicily, Sardinia, and also in Merv (Russia), and it is quite common in Palestine.—Ed.] According to Pampoukis' statistics, there occurred in Greece, among 34,937 malarial cases, 0.7 per cent. with hemoglobinuria. In Algiers Laveran saw one single case. [In India we know of three foci—(1) The Duars and Terai and Assam; (2) the Jeypore agency in Madras; and (3) the Canara district in Bombay presidency.—Ed.]

The general experience is that blackwater fever occurs almost exclusively in persons who have lived for a long time in severe malarial regions and have suffered several times from malaria. Bérenger-Féraud found, among 185 patients with blackwater fever, but one who had dwelt in the region only three months, and but ten less than a year, while 42 cases occurred in the second year of residence, 79 in the third, 37 in the fourth, 9 in the fifth, and the remaining 8 later. We may say, in general, that it is a rarity to see a person attacked within the first half year of his residence in any one of the previously mentioned regions.

This fact, confirmed on all sides, constitutes the basis for the theory, frequently suggested, that repeated infections with malaria create an individual predisposition which acts as a groundwork for the disease.

The concrete factors of this acquired predisposition have not yet been explained. Some authorities attribute it to the anemia, while others consider this of no special moment.

The clinical course, as described by the early French workers in this field, leaves no doubt that blackwater fever is an expression of malarial infection. Moreover, the blood examinations of recent years, confirming the presence of the malarial parasites in these cases, have made it absolutely certain. [We append here the result of a series of microscopic examinations made by competent observers.

Author.	Day Before Hemoglobinuria.		Day of Hemoglobinuria.		Day after Onset.	
	Number of cases.	Number positive.	Number of cases.	Number positive.	Number of cases.	Number positive.
A. Plehn	5	5	5	3	10	2
F. Plehn	0	0	21	18	10	3
Koch	5	5	8	6	6	1
Stephens and Christophers	1	1	9	2	16	0
Daniels	3	3	3	1	2	0
Panse	9	8	17	9	20	5
Total	23	22	63	36	64	11
Percentage positive	95.6 per cent.		61.9 per cent.		17.1 per cent.	

It is evident, therefore, that it is of great importance when the blood examination is made. In those cases examined *before* the onset of the attack, parasites are practically always present. They then rapidly disappear, but even in negative cases we often have evidence of a malarial infection in—(1) The presence of pigmented leukocytes; (2) an increase in the percentage of large mononuclear leukocytes. —ED.]

Yersin found, in the urine of two cases, small bacilli lying on the renal epithelium. He cultivated them and found them pathogenic for mice and rabbits. He drew from this the conclusion, hasty in our opinion, that blackwater fever has nothing to do with malaria. Further, we miss from Yersin's paper the blood-findings. Breaudat found the same coccobacilli in the urine in five cases, and identified them with Bacteria coli, while Berthier, under strict precautions, found the urine sterile.

Having thus fully determined that blackwater fever is, at least in certain cases, a malarial infection, due in most cases, but not always, to the malignant tertian parasite, it is necessary to assume that the individual predisposition has other causes than repeated malarial infection. One of these is generally considered to be the tropical climate.

In addition to these two principal factors in the creation of the individual predisposition there are probably other auxiliary ones.

As such an auxiliary factor, alcoholism has been frequently suggested, and not only chronic alcoholism, by diminishing the resisting power of the organism, but also acute alcoholic intoxication, which is not rarely immediately followed by an attack of blackwater fever.

Corre, Karamitsas, and Berthier attribute a causal rôle to cold, though the general facts do not bear them out. Their theory was probably based on the ground of Lichtheim's paroxysmal hemoglobinuria ex frigore.

Bérenger-Féraud noticed that, among the affected, there was a comparatively large number who had just taken the mercury cure, and he attributed to the mercury an injurious effect on the resisting power of the red blood-corpuscle. Again, syphilis has been suggested as the more important factor, and this conclusion becomes more probable when we recall the analogy of the paroxysmal hemoglobinuria with similar symptoms in syphilis (destruction of the red blood-corpuscles).

In addition to these the rôle of provocative agent has been often attributed to physical hardship and psychic emotion.

Moreover, the disease has been observed to break out rather commonly after change of residence. Travelers coming from the interior to the coast seem to be especially frequently attacked.

Finally, quinin plays a very important part. This drug has undoubtedly the power of producing blackwater fever in predisposed individuals. It signifies but little when we read that the inhabitants of these malarial regions have held quinin in suspicion for a long time, since it is well known that the laity are very free with their *post hoc ergo propter hoc,* and since the whole history of quinin represented one constant struggle before it was generally recognized, but when the same conclusion is reached by physicians of large experience, it is a very different matter.

The peculiar fact was first reported by Tomaselli in Catania, and soon after by Karamitsas, that there were persons who every time they took quinin, even in very small doses, manifested a severe fever paroxysm with hemoglobinuria. All these people had suffered repeatedly from malaria, or were at the time of observation in a condition of chronic infection. Some of these reacted in this way every time that quinin was administered, even after they were free from malaria for some time, while others showed only a temporary idiosyncrasy, which they lost after recovery from the malaria. Tomaselli insists that he has never met in Sicily a genuine or rather a pure case of hemoglobinuric bilious malaria, inasmuch as he has always found it manifested by patients only after the administration of quinin. Yet Tomaselli does not doubt that in other places cases of this character arise apart from the action of quinin.

Ughetti goes further than Tomaselli, and asserts that there is no such thing as febris biliosa hæmoglobinurica, and that all such cases are to be regarded as quinin intoxication.

Similar assertions have been made by Monneret, Duchassaing, Briquet, Karamitsas, Moscato, Plehn, Kohlstock, R. Koch, and others, and in fact the majority of recent observers who have had actual experience of the disease. Pellerin reported that in Guadeloupe both the public and the physicians were forced to attribute blackwater fever exclusively to the action of quinin. Cartier reported the same from Diego Suarez; more than this, the people will take no quinin on account of their fear of hemoglobinuria. Cartier also mentions that the female Creoles refuse quinin on account of their belief that it causes metrorrhagia and abortion.

Murri and Grocco have made some interesting investigations on this subject, which we will take up later. Baccelli likewise gave it his attention, and reported that among numerous cases he never met one of quinin hemoglobinuria. He contends further that quinin hemoglobinuria has nothing to do with malaria (for further details, see below). Bastianelli expresses a similar opinion.

Tomaselli, to whose investigations we are indebted for the theoretic as well as practical knowledge of the injurious effect of quinin in malarial persons, maintains that the predisposition to this quinin idiosyncrasy is congenital; further, even hereditary, for he often observed that brothers and sisters or near relatives showed the same peculiarity.

From these contradictory opinions it is evident that the rôle of quinin in the production of malarial hemoglobinuria is a complicated one, not yet fully understood. Nevertheless, several points have been brought out that may act as a basis for further investigation.

It may first be regarded as settled that cases of malarial hemoglobinuria have occurred in people who had immediately previously taken no quinin. It is also assured that there are persons who suffered from previous attacks of malaria who later, without a blood examination, to prove the continuance of the infection, manifested a hemoglobinuria with their fever paroxysm every time, or at least usually after taking quinin. This condition may be designated as postmalarial quinin hemoglobinuria. Finally, there are a large number of cases of virulent malarial infection that ran their course without striking symptoms up to the time quinin was taken, that immediately—*i. e.*, three to six hours—after the administration of this drug manifested a fever paroxysm with hemoglobinuria.

In the first two categories, that is—(1) attacks of hemoglobinuria during acute malarial infection (without quinin); (2) attacks of hemoglobinuria as a result of quinin (or, as we will see further on, even without the administration of quinin) in people who have frequently suffered from malaria, but are, for the time being, free from infection—in these two categories the mechanism of the hemoglobinuria is clear. For in category (1) we may make the parasites or their toxin, in category (2) the quinin, responsible for the destruction of the red blood-corpuscles, with subsequent solution of the hemoglobin.

The cases of the third category—attacks of hemoglobinuria during acute malarial infection, after the administration of quinin—are difficult to diagnose, for in these we cannot say whether it was the quinin that produced the destruction of the blood-corpuscles, or whether this would have taken place without its administration.

If we find, in a series of cases following the administration of quinin, that an interval occurs when the quinin is removed, this would evidently pronounce for the toxicity of the drug, but such series of hemoglobinuric paroxysms are very uncommon. What usually happens is that when a blackwater paroxysm occurs as the apparent result of quinin, further fever paroxysms either do not occur, or, if they do, may be successfully combated by quinin, without hemoglobinuria appearing a second time. This is a difficulty in the way of the quinin theory, for it is difficult to imagine that a medicament could be very toxic one day and a few days later be entirely indifferent. [The difficulty is perhaps only an apparent one, for if we assume that only a certain number of corpuscles are of such a kind that they are capable of being destroyed by the quinin, then when these (weak) corpuscles are dissolved by the quinin, it is evident that a second dose of quinin may produce no hemoglobinuria, simply because there are no suitable corpuscles to be attacked.—Ed.] In the case of paroxysmal hemoglobinuria ex frigore, as well as in the case of pure quinin hemoglobinuria, we can produce an attack at any time by means of cold or quinin respectively. Among the 35 histories published by A. Plehn, it is expressly remarked in 13 that the later fever paroxysms were cured by quinin without hemoglobinuria appearing [yet on the above hypothesis this is intelligible, and, indeed, there are facts, such as the *increased* tonicity of the blood in blackwater fever, which support this view, the corpuscles of lessened tonicity having presumably been the first to disappear. —Ed.]. According to the report of Dupuy, a dose of quinin is regularly administered to the blackwater fever convalescents coming to the sanatorium at Kita (Sénégal), in order to prevent further paroxysms, and it always has had this result. [Marchouse has recently made the very important observation that *during* the hemoglobinuria quinin cannot be detected in the urine, but that it is present later. It is perhaps justifiable to conclude that it is lack of excretion that is responsible for the hemoglobinuria.—Ed.]

Grócco reports a case in which, while parasites were present in the blood, a dose of 0.40 gram quinin per os called forth a severe paroxysm of hemoglobinuria, with a temperature of 40°, while after the disappearance of the parasites a dose of 1.50 gram quinin subcutaneously produced only a mild paroxysm. From this Grocco draws the logical conclusion that it is not the quinin itself which destroys the corpuscles in malarial cases, but a toxin produced by the parasites under the irritation of the quinin. This theory, though, fails to take into consideration that genuine parasitic reactions, as mentioned above, usually yield to quinin without the production of other symptoms.

Moreover, these cases can be, least of all, regarded as examples of the toxic effect of quinin, in which, after the administration of the drug, the paroxysm of hemoglobinuria appears, but the disease is cured. Without considering the treatment of blackwater fever, we must insist that that primary dose of quinin, whether or not it caused hemoglobinuria, surely affected the parasites and eventually brought about recovery.

As far as the etiologic rôle of quinin in blackwater fever is concerned, our own opinion is that there are undoubted cases of acute malarial infection in which hemoglobinuria is caused by the quinin; yet in the criticism of cases which show a paroxysm a short time after the first dose, none at all after subsequent doses, we must be especially careful, since there is no proof that quinin acted poisonously in these cases. In the section on Complications and Sequelæ we will return to quinin hemoglobinuria.

From the preceding it is clear what importance can be attached to the blood examination in these cases. Only by a parasitologic diagnosis is it possible to decide whether we have to do with a postmalarial hemoglobinuria produced by quinin or a paroxysm in the course of a malarial infection. The therapeutic indication in these cases can be grasped only from the positive or negative finding, and without this the patient may be injured or even his life placed in danger. (Further details in the section on Therapy.)

The frequency of blackwater fever varies with the geographic location and the season. In general we may state, with Bérenger-Féraud, that the disease is most frequent in those tropical regions which show the most extensive foci of malaria. [Further, we must take into account, in comparing different regions, not only whether the type of fever there is especially virulent; we cannot compare, for instance, the fever of tropical Africa with that of northern Italy, even if the parasite is the same, but also whether there is a susceptible population present, living under the unfavorable conditions of climate and danger of infection, such as we find in tropical Africa. —Ed.] According to his statistics, based on a large amount of material, there occur in the French West African colonies 0.28 to 53.05 cases of blackwater fever among 100 people a year, depending on the locality. The worst places are Gabun, with 53.05 per cent.; the gold coast, with 37.7 per cent.; Upper Sénégal, with 21.31 per cent., etc. According to his estimation, the average shows a morbidity of 17.81 per cent. a year. According to Davidson, there were reported in Nossi Bé, among 2600 malarial cases, 185 cases of blackwater fever, a proportion of 1:14. In Kamerun Friedrich Plehn observed a proportion of 1:11 or 12; Albert Plehn, 1:8.05. Döring had, from May 1, 1896, to February 1, 1897, in Kamerun, among 169 malarial cases, 40 (!) of blackwater fever. [Against the malarial origin of blackwater fever is generally quoted the fact that blackwater fever is unknown in India; this is, as we have seen, not true. And, again, though India is rightly designated a malarial country, it is not so in the sense that tropical Africa is. For, on the whole, it is the simple tertian parasite that predominates in India, while this parasite is exceedingly rare in tropical Africa, where the malignant tertian parasite almost exclusively prevails. Then in India we do not often have a European population living under the wretched conditions still so widely prevalent in Africa, and we see comparatively few of these malarial "wrecks" so common in tropical Africa. That this is a very important difference, we strongly believe.—Ed.]

As to the season of the year during which cases are most frequent, Bérenger-Féraud found that a much smaller number of cases occurred in Sénégal from January to June than from July to December, while on the gold coast and in Gabun the distribution over the whole year was more uniform. It is almost the unanimous opinion of writers that the transition periods between rainy and dry weather are the most dangerous.

All authorities agree as to the difference in race predisposition. Negroes show the greatest immunity, though even among them isolated cases have been reported (Bérenger-Féraud, Borius, Corre). Mulattoes too are rarely attacked. Hindus and the Chinese coolies suffer more frequently, and most frequently of all, the Europeans and the white Creoles. From this has arisen the French name, "Fièvre jaune des Créoles ou des acclimatés." According to Blanc, who collected his observations in Tongking, the Annamese are immune, while Europeans are not infrequently victims.

The principal symptoms of blackwater fever consist in hemoglobinuria, icterus, and fever. The fever may be intermittent (quotidian or tertian), remittent, or continued, though we may add that the less inclination the fever shows to intermit or remit, the more severe the attack.

Since the urine contains the principal symptoms, it is naturally of the greatest importance in the recognition of the condition. The red or black urine is usually discharged for the first time several hours after the beginning of the attack. It is rarer to find the bloody urine appear first, and the other symptoms, fever and icterus, later. Its color varies between a clear brownish-red and the translucent color of venous blood. In most descriptions it is compared with port wine, Malaga wine, or black coffee.

Omitting complications, when first passed, the urine is always clear. After standing a few hours there falls to the bottom of the vessel a muddy sediment (cloudy in its upper layers) of red or grayish-red color. Spectroscopically, this urine shows the lines of oxyhemoglobin, as Corre first demonstrated, though often, too, especially after standing some time, those of methemoglobin, and frequently of urobilin (Louvet). According to Grocco, in mild attacks urobilin alone is present.*

Berthier claims that the hemoglobin cannot be removed from the urine by dialysis, and assumes that it is not exactly in a dissolved condition, but is connected with a very fine red blood-corpuscular débris.

The reaction of the urine is feebly acid, neutral, or even slightly alkaline. The specific gravity varies considerably. According to Bérenger-Féraud, it fluctuates between 1014 and 10.35. It appears to depend, therefore, more on the concentration of the urine as a whole than on the amount of coloring-matter, which, in spite of its impressive color, considered quantitatively, is not very great. At the close of the paroxysm a large amount of clear urine of low specific gravity (108 or even under) is excreted.

During the attack the daily amount of urine is likewise very variable (it is, as a rule, increased), though it may be usually decreased, and often to a few cubic centimeters. Complete anuria for one or several days is not uncommon. Bérenger-Féraud describes a very rare case that passed, in one day during the attack, 4.5 liters. A similar observation was made by Corre.

The urine always contains albumin, and often in larger amounts than would correspond to the quantity of hemoglobin. Denozeilles determined the amount in several cases, and found it between 0.3 to 1.6 per cent.

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* For the sake of the historic interest, we may mention that the first describers of this disease attributed the color of the urine sometimes to biliary coloring-matter (Bérenger-Féraud, Daullé), as well as to the blood (Pellarin, Barthèlemy-Benôit). This explains the different names applied to the condition at various times. The demonstration of blood coloring-matter spectroscopically was made by Corre, Venturini, and Karamitsas. That it was dissolved blood coloring-matter, or, in other words, a hemoglobinuria and not a hematuria, was shown by Corre, Grennet, Louvet, and Karamitsas. (Compare Corre's work, "Traite des fièvres bilieuses," etc.)

Ordinarily the albuminuria continues a few days after the attack, when it gradually decreases. In some cases its continuance indicates the development of nephritis.

In addition to serum-albumin, peptone and propeptone have been found. The phosphates are decreased (Grocco). Bilirubin is generally absent. As long as the urine is very dark, Gmelin's test is unsatisfactory. When the amount of hemoglobin diminishes, the test is occasionally positive. Calmette claims he never succeeded in finding it.

Microscopically, none at all or only a few red blood-corpuscles are observed. The sediment consists of isolated leukocytes, hyaline and sometimes granular casts, to which often amorphous yellowish granules are attached. These granules are also found free in large numbers. [They are probably the remains of the destroyed red cells.—Ed.] Epithelium from the kidney and the urinary passages may be present in larger or smaller amounts.

Icterus is an essential symptom of blackwater fever. It is sometimes present in a slight degree during the prodromal fever paroxysm. Ordinarily it appears first with the hemoglobinuria, becomes especially evident during the hot stage, and later increases rapidly in intensity. It often continues a few days after the attack. The intensity of the icterus varies between a slight suggestion of yellow on the sclera to the most intense discoloration of the skin.

As to the course of blackwater fever, we may mention, first, that the paroxysm of hemoglobinuria itself is usually ushered in by prodromes. These consist in paroxysms of fever, which are repeated two or three days and which are often characterized by being introduced with a more or less pronounced chill. These prodromes, therefore, are differentiated from those of the ordinary tropical malarial fevers in that, as mentioned before, the latter often lack the cold stage.

Still we must add that here, too, the prodromes may occur without the chill. In this case there are malaise, pain in the limbs, and slight fever. It is rare to see the blackwater attack set in without any prodromes (Bérenger-Féraud).

We have first one to three prodromal fever paroxysms, frequently very slight, and, apart from the chill, presenting no special symptoms, then all at once the peculiar attack and the remainder of the symptoms occur.

According to the severity of the symptoms, the majority of writers distinguish mild and severe cases. Bérenger-Féraud describes four grades of severity—namely, first, mild or intermittent; second, moderately severe or remittent; third, severe or subcontinued; fourth, especially severe (fulminating) forms. This outline shows, too, the connection between the type of fever and the severity of the condition, though in this regard there are exceptions.

In the mild cases the paroxysm begins with a chill of varying severity. The patient complains of headache, constriction in the region of the liver and the stomach, and very often of lumbar pain. There is nausea, with an inclination to vomit. Vomiting soon occurs and becomes frequent, consisting first of the remains of food, later of pure green bile; yet it may be entirely wanting. The patients suffer from violent thirst, but on account of the constant nausea, dare not alleviate it.

The epigastrium and right hypochondrium are painful. Sometimes the whole abdomen is spontaneously painful and sensitive to pressure. The liver is somewhat enlarged. The spleen usually shows a large tumor (the result of earlier infection) and is always enlarged to percussion.

Constipation is common, though there is sometimes an inclination to diarrhea.

French writers mention the frequent occurrence of a colic resembling lead colic (colique sèche ou colique nerveuse des pays chauds). The abdomen is contracted, and the patient complains of continuous violent pain, yet these are the only symptoms of lead-poisoning. When this dry colic is conspicuous, the physician may overlook the hemoglobinuria and fall into serious error. Moursou's opinion that all cases of colique sèche are to be attributed to lead-poisoning is, even from his own descriptions, far-fetched.

The urine passed during the paroxysm shows the color of sherry wine, or even of pure blood, together with the other characteristics mentioned above.

Micturition is ordinarily not disturbed, yet sometimes there is a burning in the urethra. Corre several times observed priapism. The amount of urine passed at one time is usually about normal. Occasionally tenesmus *ad matulam* is present. The icterus in these cases is usually of a light grade.

After four to six hours the symptoms disappear under a simultaneous fall of temperature, which is often associated with an outbreak of sweating. The urine may show again a normal color six hours after the beginning of the paroxysm.

One single paroxysm usually constitutes the sum-total in these mild cases, yet sometimes, after regular or irregular intervals, one or two more paroxysms similar to the first occur.

When these symptoms increase in intensity and duration and are accompanied by symptoms of prostration and adynamia, the disease-picture assumes a very ominous character and we speak of a severe form. This, too, begins with a chill, intense headache, precordial anxiety, dyspnea, etc. These opening symptoms are exceedingly distressing, and from them the severe course may be conjectured.

The most distressing condition to the patient is a continued nausea and an inconquerable vomiting of bile. In addition there is a profuse diarrhea, characterized by yellowish-brown or brownish-red stools, so that the dejections may be easily confused with the urine (Bérenger-Féraud). An especially distressing singultus (of grave prognostic import) frequently comes on, which may continue day and night without relief. The thirst brought on by the fever and the great loss of fluid from the body are almost as intolerable and cannot be alleviated on account of the constant vomiting.

The tongue is covered by a thick, dirty, sometimes black coating, the result of the bilious vomiting.

The abdomen is usually tense and painful. The pain radiates from the epigastrium and the right hypochondrium to the lumbar region, or is limited to the latter.

The icterus becomes rapidly marked and may reach the highest grade. If the disease lasts a long time, it gradually decreases and gives way to a dirty leaden hue. It sometimes lasts two or three weeks.

According to Bérenger-Féraud, epistaxis is frequent, but this has not been confirmed by others. Petechiæ are sometimes observed. The urine in these cases is blood-red, and, as a rule, considerably diminished in quantity, amounting often to not more than 50 c.c. in the twenty-four hours. Complete anuria for several days is not rare. In these cases uremia is added to the other symptoms, which, as a result, frequently become worse (vomiting, singultus, diarrhea, etc.).

The general condition of the patient is very serious. At the beginning of the disease, a tormenting anxiety and restlessness appear to distress the patient through days, and prevent sleep at night.

Later the symptoms of deep prostration and adynamia predominate.

The pulse is hastened; the tension, at the beginning increased, sinks suddenly. The condition may eventually assume the whole symptom-complex of syncopal algid pernicious.

The severe symptoms continue for several days to two weeks, with more or less evident remissions. These remissions may be absent, and then the condition becomes so much the more serious. [We have summarized earlier the results of blood examinations by recent observers.—Ed.]

According to Bastianelli, the parasitologic findings in the blood vary. We may find developmental stages of the small ameboid parasites or organisms of the crescent order, or only melaniferous leukocytes. Again, there are cases in which the blood examination is entirely negative, and the anatomic investigation alone shows the signs of a previous infection by the endothelial, perilobular, and perivascular melanosis. We will discuss these latter cases under Postmalarial Hemoglobinuria.

As to the cases showing positive results in the blood examination, Bignami and Bastianelli found once the coincidence of the hemoglobinuria with the sporulation of the parasites. From this they thought it possible that the act of sporulation and the destruction of the blood-corpuscles might be associated. When the hemoglobinuria persists, though only forms of the crescent order are present, and even the spleen contains no ameboid parasites, it is possible that the destruction of the blood-corpuscles caused by the small parasites previously present continues, for reasons that we do not understand, analogously to the temperature movements not rarely observed with crescents alone. Bastianelli proposed to designate the first cases as "accessual," the second as "post-accessual," hemoglobinuria.

Shadow-corpuscles are sometimes, but not often, found free or inclosed in leukocytes. The infected red blood-corpuscles are usually not distinguishable from those of other forms of malaria, and it is only rare to find them prematurely decolorized. Bignami and Bastianelli believe that the parasites in these latter die as a result of the decolorization, and that spontaneous cure may occur in this way. A. Plehn also expresses a similar view. Unfortunately, the phenomenon of decolorization is too seldom to act as a premise for extensive conclusions.

As regards the negative blood examination in blackwater fever, little is proved, as we have seen, when the blood is not examined at the beginning of the disease, and still less when the patient has previously taken quinin.

Döring reported the findings to be almost always positive at the beginning of the attack.

The blood examinations show otherwise a striking and rapid decrease of erythrocytes, which is explained by their solution. From numerous cases in which blood counts were made I take two from Boisson. In one patient, before the paroxysm, he found 1,700,000; after the paroxysm, 670,000; in the second, before the paroxysm, 2,400,000; after, 1,600,000. These figures do not at all correspond with Ponfick's, yet the correctness of the latter's is by no means questioned, though we must assume an extraordinary rapid regeneration to explain them. The frequent occurrence of normoblasts, megalocytes, and microcytes in the blood would indicate such a regeneration. F. Plehn suggested that a thickening of the blood as a result of profuse diarrhea and vomiting must also be taken into consideration.

Bastianelli found in every case of blackwater fever a polynuclear leukocytosis. [The polynuclear leukocytes often constitute 90 per cent. of all leukocytes.—Ed.] Increase of the blood-platelets has likewise been asserted.

Examinations of the blood-serum for dissolved hemoglobin are in too small numbers to deduce conclusions of any significance. Boisson, who had the opportunity of conducting examinations accurately in the hospital at Lyons, found in one case the blood-serum reddish in color. Spectroscopically oxyhemoglobin, methemoglobin, and urobilin were seen. [On the other hand, there may be no hemoglobinemia, even while hemoglobinuria persists.—Ed.]

It is, moreover, doubtful whether in every case the solution of the red blood-corpuscles takes place in the circulating blood—that is, whether in every case a hemoglobinemia can be found in the peripheral vessels, or whether there are cases, as has been asserted, in which hemoglobinemia does not occur at any stage of the paroxysm. For these latter possible cases the hypothesis has been suggested that the destruction of the erythrocytes takes place in the kidneys.

Berthier found, in two cases examined spectroscopically, only the bands of oxyhemoglobin, while the color was the same as that of normal blood-serum, and assumes that malaria hemoglobinuria is not the result of hemoglobinemia, but of hemorrhages into the kidneys, from which the urine extracts the blood coloring-matter. We do not wish to question the renal hemorrhages (apoplexie rénal) found by Pellarin, but we do believe that Berthier took the blood from his patient at a time when it would be impossible to say with certainty that no hemoglobinemia had existed. He took the blood always several hours after the beginning of the paroxysm; in other words, at a time when the liver and kidney would already have removed the greater part of the hemoglobin. Attempts made by ourselves in several cases of paroxysmal hemoglobinuria taught us caution in this respect.

We may refer here to the similarity of the symptoms of blackwater fever with those of paroxysmal hemoglobinuria. In both we see a chill, rise of temperature, anxiety, cyanosis, and pain in the region of the kidneys as constant symptoms. It seems, therefore, justifiable to assume that in blackwater fever only a part of the symptoms are to be attributed to the toxic effect of the malarial parasites, while the others should be attributed to the destruction of red blood-corpuscles.

The duration of the disease is very variable. In mild cases we seldom see more than two or three paroxysms and often only one. In these the duration of the disease is not more than two to five days. Severer cases with subcontinued fever may last ten days, though the very severe ones, with fulminating symptoms, may produce death in two or three days. According to Corre, the duration of the favorable cases is three to fifteen days (in one case, twenty-two days); that of the fatal cases, two to twelve days.

In the majority of cases blackwater fever terminates in recovery. This is naturally preceded by a pretty long convalescence. It is needless to say that malarial cachexia follows in many cases, and these cannot, therefore, be regarded as cured.

The mortality statistics differ widely. Factors depending on the time, place, and individual seem to influence the severity of the case. How far the therapy is to be taken into consideration will be discussed in the section on Therapy.

Corre in Nossi Bé had a mortality of over 50 per cent. in cases treated outside the hospital; of 28 per cent. in hospital patients. Barthèlemy-Benôit had in Sénégal, 25 per cent.; Guiol in Madagascar, 31.6 per cent.; Cassan in Gorée (West Africa), 32.1 per cent.; Bérenger-Féraud, who took his statistics from 286 cases treated in West Africa, 66 deaths—about 23.1 per cent.; Steudel from 18 cases—17 per cent.; F. Plehn, 39 cases—over 10 per cent.;

A. Plehn, 53 cases—9.8 per cent.; O'Neill (Madagascar), 50 cases—4 per cent. Pampoukis estimates for Greece a mortality of 6.6 per cent. Ségard found the cases in Madagascar not so pernicious as generally considered.

The *exitus letalis* occurs in different ways. Sometimes the subjective symptoms improve immediately before and the patient dies unexpectedly in syncope. More frequently a typhoid condition with algid symptoms develops: Small, compressible, rapid pulse; cool skin; clammy sweat; crusts on lips and tongue; stupor and occasionally coma or convulsions (Guillaud). In other cases the skin is dry, the pulse soft and small, hemorrhages occur from the nose, mouth, or intestine, the alæ of the nose and lips become crusted, and an obstinate singultus (an especially common symptom) develops. The end is ushered in by complete or almost complete anuria, involuntary fecal evacuations, and delirium. These symptoms may continue several days. This form lasts the longest, death occurring frequently, in the second week, when the icterus may have almost disappeared (Raimond).

The diagnosis of blackwater fever is based on the cardinal symptoms—fever, icterus, hemoglobinuria—and on the presence of the malarial parasite.

Without the last, a differential diagnosis between quinin poisoning and blackwater fever is often impossible. This is especially true when quinin was administered before the paroxysm and when the disease is of intermittent type. Blackwater fever is likewise differentiated from paroxysmal hemoglobinuria only by the presence of parasites. Not much can be judged from the effect of cold, since, according to Corre, cold frequently plays an active rôle in malarial hemoglobinuria. When the fever is continued and remittent, quinin poisoning and paroxysmal hemoglobinuria need scarcely be considered.

In regions where malaria and yellow fever are simultaneously endemic, blackwater fever has been frequently, especially in earlier times, confused with yellow fever, yet the two conditions are easily differentiated if we remember that hemoglobinuria never occurs in yellow fever, and only seldom hematuria, while other hemorrhages, especially hematemesis (vomito nero), common in yellow fever, are rare in malaria. Moreover, yellow fever attacks people who never suffered from malaria; it begins without prodromes; the fever is continued; the icterus slight, and is visible first on the third or fourth day; there are two periods of the disease to be recognized, etc. Finally, in addition to all these clinical symptoms, there is the blood examination, with its positive conclusions.

Confusion of blackwater fever with acute yellow atrophy of the liver, phosphorus-poisoning, and Weil's disease is easily avoided.

The prognosis is serious. When the initial symptoms are not too severe; when the patient is healthy and his resisting power has not been injured by alcohol, syphilis, or other disease, the prognosis is more favorable. In the course of the disease an intermittence of the paroxysms is to be hoped for, since a continuance of the fever and the other symptoms aggravates matters.

Persistent vomiting, lasting several days, is dangerous, on account of the impossibility of nourishing the patient. If profuse diarrhea is present at the same time, the rapid enfeeblement is all the more to be feared. Sudden sinking of tension with increased frequency of the pulse and singultus are to be regarded as inauspicious symptoms. Algor and coma are likewise ominous. Anuria for several days is very serious, yet not necessarily fatal, since secretion not rarely begins again. Polyuria is usually a favorable sign, yet there are cases (Bérenger-Féraud, Corre) in which a fatal termination occurred in spite of a marked polyuria—possibly even as the result of it.

The intensity of the icterus, as well as the more or less dark color of the urine, is of no prognostic significance, though it is important to watch for symptoms of acute nephritis, since this makes the prognosis worse.

Complications, Sequelæ, and Convalescence.—We have already stated that in severe cases of blackwater fever other pernicious symptoms, like algor, collapse, coma, and convulsions, sometimes occur, and usually with a fatal result. These conditions are not to be regarded as true complications, but as further expressions of the malarial infection. When anuria occurs, the suspicion of an acute uremia naturally arises, and in this case we may speak of a complication. The observation of the clinical symptoms *in vivo* under these circumstances, is of less aid to a proper conclusion than the postmortem finding. During the course of the disease the only symptom indicating the condition would be the occurrence of urea in the vomit. Guillaud has described three cases of blackwater fever with severe uremic and nephritic symptoms. The autopsy showed in each case an acute nephritis.

Among the hemorrhages, petechiæ, retinal hemorrhages, and epistaxis are the most frequent. Less common are melena, hematemesis, and hemorrhages into the pleura and the pericardium. According to Steudel, pleuritis sicca is a frequent occurrence.

Among the sequelæ, severe anemia and cachexia must be mentioned. The stomach frequently continues very sensitive, and as a result of the persistent bilious vomiting there may be loss of appetite and nausea. Intestinal action is likewise frequently altered. *Colique sèche* is occasionally seen.

In the great majority of cases the kidneys endure without injury the irritation produced by the hemoglobinuria, though acute nephritis sometimes develops as a consequence. This may manifest itself immediately after the attack by the occurrence of numerous epithelial, granular, and corpuscular casts in the scanty albuminous urine (cases of Guillaud, Kelsch and Kiener), or it may develop and become evident only after the disease has passed. In these cases the question must always be considered whether the individual had not nephritis previously.

Convalescence is usually protracted on account of the severe anemia and the gastro-intestinal disturbances. Chronic malarial cachexia lasting throughout life is not infrequent. After mild attacks the general health may be at once restored.

For the pathogenesis of blackwater fever we refer to the proper section. Here we will only say that the essential factor consists in a sudden enormous destruction of red blood-corpuscles and their simultaneous solution. That the number of destroyed erythrocytes must be uncommonly large to permit the blood coloring-matter as such to pass the kidneys is evident from Ponfick's experiments and from the blood examinations.

According to Ponfick's experiments, about one-sixth of the entire number of red blood-corpuscles must be destroyed in order to produce hemoglobinuria. If a smaller number succumb, the liver activity is sufficiently great to use them up in the elaboration of bile.

The final cause of the destruction of the blood-corpuscles is unknown. We mentioned previously that the parasites found in blackwater fever are in no way distinguishable morphologically from the parasites of the ordinary estivo-autumnal fevers. Whether they are more virulent or have the power to excrete a specific hemolytic poison are conjectures that cannot at present be substantiated.

Blackwater fever is evidently not more severe on account of a greater number of parasites or higher temperatures, because it does not manifest these.

Remembering that only such persons are affected as have suffered repeatedly from malaria and have lived for some time in tropical malarial regions, we are forced to attribute the destruction of the red blood-corpuscles to factors resident in the individual, possibly in the blood-making organs, acting in association with climatic conditions. The predisposition to this disease produces no characteristics which we can yet recognize, for it is not even limited to anemic individuals.

As an example of a mild case, we take the following from O'Neill*:

Jacques Reneau, aged thirty-four, marine, has lived three years on the African coast and eleven months in Rio-Nûnez. After his arrival in Boké he had an attack of intermittent fever. The day before admission to the hospital, he had a fever paroxysm, for which he took 0.80 quinin with ipecac.

January 10, 1868: 10 A. M.: He entered the hospital with a chill which lasted half an hour. He stated that he had had bilious vomiting and bloody urine. Face pale, scleræ slightly yellowish, pulse hard, tension high—114. Temperature in the axilla, 40.5°.

Prescribed 1.5 calomel to be taken within ten minutes, infus. flor. aurant. and an emollient cataplasm to the abdomen.

4 P. M.: During the day three times bilious vomiting and three bile-stained stools. Urine large in quantity, of port-wine color. Pain in the lumbar region and epigastrium. Headache in the top of the head. Intense thirst. Pulse dicrotic ("vibrant")—113. Temperature in the axilla, 41.2°. Ordered iced lemonade.

8 P. M.: For the last three-quarters of an hour sweating. Urine yellowish, cloudy, still containing some albumin. Temperature in the axilla, 38.5°; pulse, 85. Ordered lemonade, 2 gm. quinin sulph. in solution to be taken within two hours; dilute wine; cold bouillon.

January 11: 7 A. M.: During the last hour a new paroxysm. Saffron-colored icterus. Urine very frothy; port-wine color. The chill was slight and lasted only a few minutes. At the time of the visit the temperature was 40.9°; pulse, 112. Nausea and bilious vomiting, girdle pains. Prescribed iced lemonade and an ice-bag to the epigastrium.

4 P. M.: Skin somewhat moist; pulse, 102; temperature, 39.4°. Prescribed quinin sulph., 1.0; syrup. diacodii, syrup. aurant., āā 30.0, to be taken in the evening. Iced drinks.

9 P. M.: Complete apyrexia. Urine yellowish, cloudy. Quinin and drinks were well borne.

Prescribed diluted wine, broth.

January 12: 7 A. M.: Passed a pretty good night, complains only of weakness and vertigo. Prescribed quinin sulph., 1.20 in 24 pills; chocolate, bouillon, Bordeaux wine.

January 13: 7 A. M.: Apyrexia; patient desires to eat.

Prescribed quinin sulph., 1.0 in 20 pills. "*Régime réparateur.*"

Boisson reports a rapidly fatal case with coma†:

D., aged twenty-three. From the Thirtieth Artillery Squadron. No hereditary complaint. At the age of twelve, typhoid fever; after his arrival in Madagascar, sunstroke, which kept him in the hospital for five days in a very severe condition. Remittent malaria for the first time toward the end of June; later, numerous intermittent attacks at irregular intervals, during which the fever was combatted with quinin. On September 27 he was sent to a sanatorium, where he remained a month, in order to recuperate.

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* Obs. iv, p. 27.

† Obs. iii.

On admission to the Hospital Desgenettes (Lyons), December 7, he was weak and anemic, though he had lost no flesh. The liver was scarcely enlarged; the spleen extended beyond the border of the ribs about 3 cm. Neither sugar nor albumin in urine. The digestive, circulatory, and nervous systems showed nothing pathologic.

During the month of December, he had, on the sixteenth and on the nineteenth, fever paroxysms of moderate severity lasting about six hours each.

December 26: Patient complained of headache and diarrhea. On December 28 he was in an excitable condition and very restless at night. During the afternoon of December 30 he had a fever paroxysm that began with a violent chill. Temperature at 2 o'clock, 41.8°. The skin rapidly became yellow. At 6 o'clock temperature, 41.7°. The scant urine was intensely red from hemoglobin, but contained no erythrocytes. At 9 o'clock in the evening, coma. Extremely little urine, stained very dark by hemoglobin, containing considerable albumin, granular casts, but no trace of bile-pigment.

The coma persisted through the night, and the next morning (December 31), at 7 o'clock, the patient died.

The autopsy showed only the signs of malarial infection.

The following is a severe case, terminating in recovery, taken from Albert Plehn*:

M., carpenter, very robust. For the last ten months (since November, 1894) has had, in Kamerun, very many severe fever paroxysms which were treated in the ordinary way with 1.0 to 1.5 gm. quinin after every fall of temperature.

In June, 1895, choleraic attack, with algor and severe collapse. Since then a paroxysm about every fourteen days—one on September 23, 1895.

September 23: 7 A. M.: Temperature normal; general condition good; was given 1.5 quinin.

10 A. M.: Chill, high fever, black-red urine.

4 P. M.: Urine of normal color and free from albumin, after which it continued so.

September 28: He rose from bed.

September 30: Discharged. Hemoglobin, 78 per cent.

October 7: Came again to the hospital after a fever paroxysm. Temperature, 38.5°.

October 8: 7 A. M.: General condition good; temperature normal, 1.0 quinin. At 12 noon, chill; temperature, 39.3°; excruciating cardialgia; bilious vomiting. At 3 P. M.: 200 c.c. dark-red urine; sp. gr., 1020; passed in drops, accompanied by intense burning in the urethra. Boiling with acetic acid coagulated the urine almost solidly. In the thick sediment numerous finely granular casts and kidney epithelium, but no blood or pus. Morphin, hot poultices. In the evening, condition improved. Temperature, 38°; 160 c.c. urine, with the same characteristics as at 3 P. M.

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* *Loc. cit.*, case 24.

October 9: During the night, no sleep.

4 A. M.: Violent chill, high fever, renewed oppression, vomiting. Urine like yesterday, 750 c.c.; sp. gr., 1012.

7 A. M.: Temperature, 39.3°; sweating. After a long search, one endoglobular parasite, about one-fifth the size of a blood-corpuscle, was found.

10 A. M.: The scanty urine appears like pure, venous blood; temperature, 38°.

11 A. M.: Chill; temperature, 39.3°.

12 M.: A very profuse sweat.

2 P. M.: 550 c.c. urine, with characteristics unchanged.

4 P. M.: Temperature, 39.8°; the sweating continues.

9 P. M.: Temperature, 39.5° to 38.6°; pulse, 132; 755 c.c. urine. The anemic hue of the skin has given way to an icteric discolorization. Burning on micturition has ceased.

October 10: 6 A. M.: Fever throughout the whole night, but no chill. Extreme anemia; severe icterus; 1100 c.c. dirty, brown-red urine.

12 M.: Temperature, 39.3°; pulse, 132; 620 c.c. urine; sp. gr., 1012; containing one-half, by volume, of a dark-brown precipitate. Hemoglobin, 21 per cent.

3 P. M.: Temperature, 37.5°.

6 P. M.: Temperature, 37.4°. Restless, considerable vomiting; pulse, 128.

9 P. M.: Temperature normal; intense exhaustion. Pulse, 128; urine, 1420 c.c.; clear ruby red.

October 11: Vomiting has ceased. Milk and egg in clyster. Highest temperature, 37.9°. During the day, over 3000 c.c. straw-yellow urine; sp. gr., 1013. Hemoglobin, 14 per cent.

October 12: 6 A. M.: Temperature, 38°; pulse, 132. Large amount of urine; sp. gr., 1012; still containing a trace of albumin.

3 P. M.: Temperature, 39.6°. No endoglobular parasites. Marked leukocytosis.

6 P. M.: Unchanged.

October 13: Morning temperature, 38.6°.

3 P. M.: Temperature, 39.3°; the pulse fell temporarily to 116 but fluctuated generally between 128 and 140. Hallucinations. No parasites could be found in the blood, and no pigment in the leukocytes. Large amount of straw-yellow urine, sp. gr., 1013, that showed, on boiling with acetic acid, only a trace of albumin. Hemoglobin, 14 per cent. Evening, condition better; during the night, fever.

October 14: Morning temperature temporarily 37.6° and 37.4°; evening, 39°; pulse, 138. Sweat promoted by a large, golden-yellow stool. Spleen extends beyond the border of the ribs two finger-breadths. Liver not enlarged. Icterus gradually disappearing. General condition always best when temperature highest. Alcohol; lots of milk, which is no longer vomited.

October 15: Temperature, morning, 39.8°; pulse, 140. In spite of this the strength has decidedly increased. Hemoglobin, 18.5 per cent.

12.30 P. M.: Profuse sweat. Temperature, 39°. Red blood-corpuscles vary in size from one-third to three times the normal. Even unstained, the megalocytes show large round nuclei. Typical endoglobular parasites could not be found. Whether isolated pigment-granules were seen in a few leukocytes is uncertain. The spleen is somewhat smaller.

October 16: 8 A. M.: Temperature, 38.8°; 1.0 quinin. This was suggested to the patient as opium, and he slept—for the first time in ten days—for three hours.

12 M.: Temperature, 39.4°; pulse, 148. Continues to take nourishment well. In addition to 5 to 6 liters of milk, eggs, ham, bread, and 2½ pints of wine a day.

6 P. M.: Temperature, 38.7°; pulse, 124. In the evening, 0.5 quinin.

October 17: Feels considerably better. Temperature, 38.7°; pulse, 124.

8 A. M.: 1.0 quinin. Sleep.

Evening: Temperature, 38°; pulse, 104; hemoglobin, 30 per cent.; 0.5 quinin.

October 18: Highest temperature, 38.3°. General condition much better.

October 19: Temperature normal.

October 21: Quickly progressing convalescence. Hemoglobin, 34 per cent. The nucleated erythrocytes have disappeared. The patient had complained for some days of visual disturbances.

October 24: Ophthalmoscopic examination of the eyes showed bilateral retinal hemorrhages. Hemoglobin, 42.5 per cent.

October 30: The purple-reddish discolorations of the retina have taken on a whitish color. Visual power restored. Hemoglobin, 45 per cent.

October 31: Temperature over 39°. The general condition but little disturbed; only appetite less.

November 1: Temperature scarcely exceeded 38°. Hemoglobin, 43 per cent.

November 2: In the morning, several attacks of bilious vomiting. Temperature, 40°. In the unstained blood a few very small ring-formed parasites. Evening temperature, 38°; 1.0 quinin.

November 3: Temperature, 38.2°.

9 A. M.: Temperature, 37.6°. In the blood, no more parasites.

10 A. M.: 1.0 quinin.

November 4: Morning, 1.0 quinin. Remained apyretic for the first time.

November 7: Hemoglobin, 53 per cent. In the course of November the patient had one other paroxysm, with a rise of temperature to 40°. Since only one generation of parasites was present, the infection was definitely cured by 1.0 quinin. Subsequently the patient took, every five days, 0.5 quinin, and remained apyretic until he returned to Germany in December.

PNEUMONIC SUBCONTINUED.

(Syn., Fièvre Intermittente ou Rémittente Pneumonique; Accès Dyspnéique.)

It is rare to see, in the course of an acute malaria, symptoms on the part of the respiratory tract that would justify this name. Some observers of considerable experience deny their occurrence absolutely (Colin, Roux).

Baccelli, Kelsch and Kiener, and more frequently the older writers, have, nevertheless, described a pneumonic subcontinued, and though the observations of the older writers may be questioned on account of the lack of proper methods, we accept those of Morton without hesitation*: "Febris intermittens primo insultu peripneumoniam acutissimam simulans."

The disease begins with a severe chill, rapidly rising temperature, and a violent stabbing pain in a circumscribed area of the thorax. The marked dyspnea, cyanosis, and especially the orthopnea are striking. Percussion of the thorax elicits a normal note, and only rarely a small area of circumscribed dulness. An osculation discovers fine moist râles over one whole lung; rarely localized. The breathing is usually vesicular, never bronchial. Vocal fremitus is unchanged.

The cough is dry and short; expectoration, wanting or scanty. When present, it consists of hemorrhagic clumps or of a tenacious, sanguinolent mucus. The condition persists as long as the fever paroxysm and ceases with it. The objective symptoms also disappear with the fall of temperature.

With a relapse, the whole symptom-complex may recur. In this case the pulmonary affection may be in the same or a different location. The objective symptoms, excepting the dyspnea, are sometimes entirely wanting.

With all its violent symptoms it usually runs a favorable course, yet cases with a fatal termination during a paroxysm have been observed.

MIXED INFECTIONS.

We previously stated that parasites of the first and second group may be found simultaneously in the blood, and gave examples of such cases.

Apart from the more frequent irregularities in the fever, these mixed infections present no particular clinical characteristics, and we will, therefore, refrain from a detailed discussion.

These cases are not very frequent. Thayer reports that in Johns Hopkins Hospital, among 1618 malarial patients, only 31 showed a mixed infection. In the majority of these the ordinary tertian parasites were associated with those of estivo-autumnal fever.

Experiments on mixed infections were done by Di Mattei. He injected patients manifesting one species with blood containing a second species (quartan parasites and crescents). He found, remarkable to say, that the new parasites just introduced supplanted the others and produced a corresponding type of fever.

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* *Loc. cit.*, p. 246.

A few observations indicate (Livio Vincenzi) that the two different species may alternate in causing fever symptoms, which would seem to show that one species is in a condition of latency while the other thrives. It is, therefore, impossible to exclude mixed infection by one examination of the blood.

LATENT FEVERS.

When the fever is absent or insignificant, we consider the malaria latent. The syndrome of such a case frequently rouses less a suspicion of malaria than of the disease imitated by the symptoms.

We must confess that this separation of latent fevers is scarcely justified. The possibility of diagnostic error should not be regarded as a principle on which to base a division, and if it were, all forms of pernicious fever should be placed in the category of latent fevers.

Formerly latent fevers comprised those malarial diseases that ran a completely apyretic course, and it was thought that this was a sufficient basis for classification. Apart from the fact that the presence or absence of fever makes a very weak foundation for a classification, the thermometer has shown that the apyrexia was only apparent, and that in almost all these cases there was an elevation of temperature of from 0.5° to 1.0° and over (Jaccoud). With this discovery the principle fell to the ground, yet the group of latent fevers has been preserved, even though it thrives with difficulty.

The broad, almost immeasurable, field of latent fevers described by Alibert, Bonnet, Griesinger, and others contracts every year. It is especially striking how little has been said about latent fevers since Laveran's discovery. This was surely the time to diagnosticate them as true malaria, yet, instead, we find only isolated reports of examinations, not a few of which were negative. The last word is still to be spoken, though it seems to us to-day as if the days of latent fevers were passed.

We will here discuss, first, those facts which stand under a modern criticism, and later the assertions which require corroboration. We may state at once that latent fevers belong among the rarities, and that, remarkable to say, we have almost no examples from severe tropical regions.

During his five years' residence in Algiers Laveran did not observe a single case, although he had the opportunity of treating hundreds of malarial infections of the most different kinds. In contrast to this Bernhardt, in Berlin, observed and treated 20 to 25 cases (trigeminal neuralgia).

Whether latent fevers are more common in cold latitudes than in the severe malarial regions of the south we cannot say. Their relative frequent occurrence in certain localities is striking. In recent years several interesting publications have come from the Caucasus (Triantaphyllides, Zakhariane, Kondriourzkoff), which are especially valuable since the observations are supported by positive blood examinations. Zakhariane had, among 320 soldiers, 148 cases of malaria, of which 27, or 18 per cent., were latent, an enormous figure in comparison to other malarial regions. The so-called latent fevers are produced by parasites of the first as well as the second group.

The **symptoms,** as a rule, are typically intermittent. The most frequent form is the quotidian, the tertian comes next, and the least frequent is the quartan. Continued and remittent symptoms have likewise been observed, though even more rarely. Those affected have usually suffered previously from ordinary malaria or show signs of cachexia. It sometimes happens that normal attacks alternate with latent ones—for instance, after an ordinary tertian the relapse occurs in a latent form.

According to Griesinger, it is particularly irritable people, especially after the fortieth year, who manifest latent attacks. The paroxysms similar to the ordinary malarial paroxysms usually occur in the forenoon hours, and last only a short time—one-half to four to six hours.

Sometimes only one definite local symptom is present; again the principal symptom is ushered in by malaise, horripilation, and yawning, and is followed by sweating. The spleen may be enlarged, but this is not usual. The different manifestations, in order of frequency, are:

Neuralgia.—This is the most common and least contested form of latent fevers.

The neuralgia occurs most frequently in the trigeminal nerve, especially its frontal branch, though occasionally in the infra-orbital and mandibular branches. Intercostal and occipital neuralgias, sciatica, hemicrania,* and other complicated neuralgic symptoms, as cardialgia, angina pectoris, and enteralgias, have been much less frequently recorded.

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* For the sake of the historic interest, the personal anamnesis of the celebrated Richardo Morton is here introduced (Pyretologia, Exercitat i, Cap. ix, Historia xxvii): "Anno 1690 a frigore suscepto, Ego ipse, ad quatriduum, insolito faciei calore periodico, præsertim a pastu, affectus sum. Dein per tres vel quatuor dies con-

The paroxysms of trigeminal neuralgia are often accompanied by a circumscribed flushing and slight swelling of the forehead near the point of exit of the nerve-branches. To this are not infrequently added injection of the corresponding eye and increased excretion of tears, associated with photophobia, nausea and vomiting (ophthalmie intermittente). After the termination of the paroxysm sweating may occur on the previously flushed places.

I have seen two cases of such supra-orbital latent forms. One was a gentleman of forty-five, who suffered, shortly before, from tertian, and who now manifested daily, exactly at midday, a latent paroxysm, accompanied by more or less nausea. The ramus frontalis was not sensitive to pressure. Immediate cure followed the administration of quinin.

The second was a man of fifty who had frequently before suffered from fever paroxysms, looked very cachectic, had a large splenic tumor and edema of the legs. He manifested daily, about 4 o'clock in the afternoon, a right-sided frontal headache that continued two to three hours. In the blood only a few crescents were found. During the pain the temperature rose each time to 37.8° to 38.2°. After the treatment with quinin and iron the paroxysms disappeared.

Duboué (de Pau) described a case of sciatica lasting several weeks which yielded to quinin and which he considers as malarial sciatica. In this case the pain was continuous, or at least remittent.

In regard to the diagnosis of malarial neuralgia, we must insist that neither the intermittence of the paroxysms nor the result of

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tinuos Hemicraniam molestam, sinistram capitis partem occupantem, ab octava hora matutina ad quintam usque Vespertinam protensam, quotidiæ patiebar. Quoad cætera firme valebam, et, cum appetitu integro, muniis solitis fungebar. Quandoquidem autem hunc morbum, antehac in aliis, non obstane trepetita Venæsectione, applicatione Vesicatoriorum, Cucurbitularum, Fotuum, Errhinorum, Masticatoriorum, et exhibitione methodica Catharticorum, Emeticorum, cæterumque idgenus, ad mentem Veterum, valde Chronicum et contumacem sæpius observassem; atque molestum hoc Symptoma a fermente febrili delitescente subortum esse, suspicatus essem utut nulla febris præsentis indicia apparerent. Post extractionem unc. XII Sanguinis e brachio sinistro, pulveris febrifugi unc. I spatio biduo devoravi. Postquam Corticis drachm. V absumpsissem, dolorem multo mitiorem, die sequenti (periodice licet et designato tempore recurrentem) passus sum. Penso vero absoluto, die proximo prorsus liberatus sum. Post tres autem hebdomadas recrudescebat dolor (sicuti in febre Cortice curata solet) quem non sine (Chinchina jam superare potui, quippe vegetam et genuinam penes me tum temporis non habui. Repetito autem Cortice post duas hebdomadas, prophylaxeos gratia, huiusque, sine quocumquo alio medicamento exhibito, optima valetudine utor."

quinin treatment proves with certainty the existence of malarial infection. It is well known that the most different kinds of pain, whether genuine neuralgias or pain due to other causes, show a pronounced tendency to intermit. I recall only the nightly pains in the bones of syphilitics. A short time ago I saw a woman with a sarcoma of the sternum who suffered from paroxysms of exquisite intermittent pain in the region of the tumor, without any sign of malaria. To what extent a conclusion can be drawn from the region of the pain I leave to the judgment of every intelligent physician.

The parasitologic investigations in relation to this disease are extremely limited in number. Sakhariane found in these cases only a few parasites in the blood; Loeza (Mexico) reports that in several cases he found no parasites at all. Whether in case of a negative finding—provided that the blood examination has been properly carried out—we may still adhere to the diagnosis of malaria appears to me questionable.

Pareses.—These are among the rarest expressions of latent malaria. I find one single positive case in Marchiafava and Bignami.* This occurred in a man of middle age, admitted to the Hospital S. Spirito (Ward Baglivi) on September 26, 1899. He was extremely weak, very pale, and complained of headache. He had no fever, the temperature being rather subnormal. The spleen was impalpable. A few hours after he was put to bed he lost consciousness. Examination showed a left-sided hemiplegia, with simultaneous facial paralysis, hemianalgesia, and abolition of reflexes. The temperature remained subnormal. An accurate investigation had failed to explain the condition, when the blood was found to show the presence of extremely numerous ameboid parasites, the majority of which were non-pigmented. Quinin was injected, and two days later the man had recovered, though he still remained very anemic.

In this case the highest temperature during the acute infection occurred during the night from September 25 to 26, and was 37.9° (in the rectum). The cerebral symptoms recovered rapidly and left no trace. The number of red blood-corpuscles on September 26 was 1,950,000.

Motor irritative symptoms are likewise very rare. Heidenhain saw in one case twitchings of the left arm and leg occurring with a tertian type; again, a case with twitchings of the masseter in association with frontal neuralgia.

Attacks of *vertigo* were reported by Triantaphyllides; attacks of anxiety, by Heidenhain.

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* *Loc. cit.*, p. 135.

Relatively more frequent are symptoms of *gastro-intestinal catarrh.* Among Zakhariane's 27 cases, 19 were associated with diarrhea. Triantaphyllides observed 11 cases of chronic diarrhea as the result of latent fever, and in the majority of these the blood examination was positive. A splenic tumor was only four times perceptible.

Bronchitis was observed by the same writer. It usually occurred without a splenic tumor, and always with non-pigmented parasites. The bronchitis failed to show any type and changed its location.

Exanthemata.—Mention has been made of several cases of urticaria in association with ordinary paroxysms; a few have also been reported in connection with latent malaria (Scorczewski, Zeissl, Kaposi, Neumann, Völcker, Brocq, and others).

The reports of herpes zoster as an expression of malaria are not convincing (Masson, Moursou, Girard, Winfield).

Other syndromes described as latent malaria seem only half convincing, as typical anesthesia, convulsions* (sneezing, vomiting, hiccup, coughing, torticollis, tic, chorea, and hysteric convulsions), paralysis of the special senses (as typical amaurosis, amblyopia, anosmia, and deafness), sleeplessness, psychoses,† hemorrhages from different organs, angina pectoris, asthma, edema, intestinal colic, vomiting, discharges of gas from the mouth or anus, coryza, neuralgia of the pharynx, of the testicle, of the urethra, of the uterus, angina, etc.

To demonstrate the relative frequency of the different forms we will quote Zakhariane's statistics. Among 27 cases there were 19 with gastro-intestinal symptoms, 2 with palpitations, 2 with angina pectoris, 3 with cephalalgia, 1 with coryza.

As a curiosity, we may add that the older writers, in their credulous way, reported a typical loquacity, even more an intermittent speech in rimed verse, as an expression of latent malaria.

It is contrary to common sense when croupous pneumonias, meningitis, etc., are reckoned among the latent fevers (Tartenson).

To whomsoever is interested in the literature of latent malaria we recommend the works of Morton, Griesinger, Hertz, Bonnet, Duboué (de Pau), Dangerville.

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* It is possibly worth while mentioning a case published by Faivre ("Jour. de méd. de Bordeaux," September, 1895), and quoted by Laveran, of a soldier with malarial cachexia who manifested very painful cramps in the calves of the legs, associated with fever and sweating. Recovery followed quinin.

† Celsus mentions (Lib. iii, Cap. xviii) the occurrence of intermittent psychoses. He designates the condition phrenitis, and says: "Levatoque accessionis impetu, protinus mens redit."

ACUTE MALARIA IN CHILDREN AND OLD PEOPLE.

Mention has been made in a previous section that children show a special susceptibility to malaria. They may be infected any time after birth; in fact, not a few cases have been recorded in which the symptoms were absolutely diagnosed during the first days of life. For the transference of the disease *in utero* and by the mother's milk see another section.

Some careful observers assert that malaria is more frequent in children than in adults, and that, at the beginning of an epidemic, the children are attacked first (Griesinger, Boudin, Schramm, Baur, Pepper, Nègre, Pellereau, etc.).

From the mortality statistics of malaria during the years 1887–1893 (inclusive), in Boufarik (Algeria), given by Nègre, we find that 62 adults and 115 children succumbed to the disease.

Still other writers (Dwight, Chapin, Osler) affirm that children are seldom affected. This difference of opinion may be due to the circumstances that malaria in children, especially under two years, readily escapes detection; that in cities malaria has fewer victims than in the country, and that city children ordinarily pass the greater part of the day in dwellings, and are, therefore, relatively better protected. According to Bohn's wide experience, children from two to seven years of age are the most frequently attacked.

The symptoms of malaria in children, especially under two years of age, differ in many respects from those observed in adults.

This subject has been studied particularly by Bohn, to whom we owe the best work. Among the French who interested themselves were Grisolle, Jules Simon, Bossu, Galland, Benoit, Nègre, and others; among the English, Thomas, Cheadle, and Kingsley. Yet the older writers did not overlook it, as is readily seen from the complete anamneses of Morton and the references in Sydenham and Torti.

All authorities agree that children show most frequently the quotidian, less frequently the tertian, and very rarely the quartan type. In tropical and subtropical regions the quotidian and subcontinued remittent types are most commonly observed.

The paroxysms occur, according to Bohn, usually between midday and midnight, while in adults the other half of the day predominates. According to the same writer, the disease begins not infrequently with the general symptoms of a continued or remittent, from which, after a few days, the typical fever develops.

We will consider, first, the typical paroxysms in children under two years of age.

The cold stage is either wanting entirely or is of so short duration as to escape observation. Only rarely is it well developed. According to Jules Simon, it lasts only a few minutes—seldom a quarter of an hour. If the child is seen at this stage, the following is observed: The face is pale, somewhat cyanotic, cool; the hands and feet are likewise cool. The skin is wrinkled; the body generally shrunken; respiration and pulse are very much hastened; yawning is frequent and vomiting is not rare.

Instead of the ordinary cold stage, Bohn observed "drowsiness, stretching of the body, yawning, trembling of the extremities, and convulsive movements of the ocular muscles; the last two especially in nurslings."

The hot stage, which is the most characteristic feature, follows. The skin is hot and flushed; the child is restless, cries for the breast frequently, or is drowsy and sleeps the whole time. The sweating stage is usually only suggested by a slight moisture on the extremities or the back of the head. There is rarely profuse perspiration. The whole paroxysm usually lasts four to six hours, but it may last twelve hours and even more.

During the interval the children are often irritable, without appetite, restless, sleepless, though sometimes none of these symptoms appears.

Herpes labialis and urticaria are frequent. Boïcesco and Moncorvo, and before them Bohn, observed several times the occurrence of an eruption simulating erythema nodosum. This appeared in painful hard nodules on the extremities, about the size of a silver dollar, which became red and swollen during the paroxysms.

Cheadle frequently observed a scarlatina-like eruption, localized principally to the neck, chest, and abdomen, which he never saw in adults. Similar erythemata were seen by Handfield Jones; in one case three or four times a day an intense redness covered the whole body of the three-year-old child.

The spleen is usually enlarged. The contradictory observation of Ferreira provokes doubt as to whether all the cases reported by him were actually malaria. Still we must confess that there are isolated undoubted observations of cases without splenic enlargement.

Bohn found a splenic tumor in every case, and attributed a greater diagnostic importance to this symptom in children than in adults. According to him, the spleen must often be sought, posterior to the axillary line or high up on the chest-wall. The enlargement is frequently associated with sensations of compression or stabbing pain, which increases in intensity during the hot stage. This, taken together with the commonly occurring bronchitic symptoms, may lead to confusion with pleurisy or pneumonia.

The splenic tumor is, as a rule, very sensitive to pressure.

After the occurrence of several paroxysms, a marked anemia sets in. With this we never fail to find a large spleen, which extends not infrequently to the umbilical region.

Among the associated symptoms, diarrhea is important. It may be extremely profuse. It usually sets in at the beginning of the paroxysm, persists throughout it, and sometimes after it. During the apyretic interval it is usually absent, or at least lessened in severity (Cantenau). The stools are either yellowish or greenish in color.

According to Bohn, the paroxysms are sometimes introduced by violent choleraic diarrhea with rapid collapse; sanguinolent stools point especially to malarial infection. The vomiting is sometimes so continuous that it threatens life; it may even persist during the intervals.

Icterus has been observed, especially in the tropics; likewise, hemorrhages into the skin in the form of petechiæ, as well as hemorrhages from the mucous membranes, particularly the nose.

Eclamptic convulsions may occur at any stage of the paroxysm. They affect all the muscles of the body, and last minutes, or, with intermissions, even hours.

They usually appear during the hot stage; less commonly at the beginning of the paroxysm, during the cold stage. In infections with parasites of the first group the convulsions are probably an expression of that irritability of the central motor region such as children manifest in different acute infectious diseases. In infections with parasites of the second group they may be due, as in adults, to the distribution of parasites in the internal organs, especially the brain.

Bohn's cases rarely manifested only one convulsive seizure, but usually three, four, even six or seven, within a few hours. These convulsions were always associated with fever.

There is reason to affirm, with Bohn, that the convulsions cannot always be attributed to the same cause, for at one time they may be expressions of motor irritability; again, genuine epileptic attacks, excited by the fever paroxysm.

Bronchitic and bronchopneumonic symptoms are less frequent than the gastro-intestinal and nervous.

As Bohn has observed, a previously existing bronchitis or laryngitis may be rendered considerably worse by an attack of malaria. The child may suddenly present symptoms of a genuine croup or a threatening diffuse bronchitis on the addition of the fever paroxysm to a scarcely noticeable catarrh of the larynx or bronchi. The splenic tumor and the intermittency of the paroxysms will aid in the diagnosis.

In tropical regions pernicious forms are seen in children as well as in adults. The eclamptic pernicious is observed most frequently; more rarely, the pure comatose form.

Algor is not infrequent and usually proves fatal. Diaphoretic, choleraic, typhoid, and pectoral forms have been occasionally seen and described (Benoit, Nègre).

Unfortunately, but very few blood examinations have been made so far, and consequently not all the cases reported can be considered malaria.

In children over two years, and especially in those over five, the fever paroxysms are very similar to those of adults, so that nothing further will be said about them.

As an example of an infantile pernicious we introduce the following history from Nègre*:

> In August, 1891, I was called, about 10 o'clock in the evening, to visit the child of Mrs. B., on account of convulsions and restlessness. I found a child of one and one-half years, well developed, in violent convulsions, completely unconscious, the pupils fixed, dilated, irresponsive to light, the thumbs shut in the hands, the face grimacing, the abdomen drawn in, the arms and legs flexed, contracted, and twitching violently, respiration slowed, intermittent, teeth pressed together, and froth issuing from the lips.
>
> For moments at a time the twitchings ceased, when the child appeared as if in coma, with respiration suspended and the pulse scarcely palpable. Two to three seconds later true convulsions of the muscles would begin again.
>
> This condition continued about half an hour. Ten minutes after my arrival the convulsions ceased and gave way to coma. The mother said that the child was healthy from birth, and that neither she nor her husband had had the fever. About 7 o'clock in the evening the

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* *Loc. cit.*, p. 53.

child had refused nourishment, and had fallen into a deep sleep, during which the paroxysm came on suddenly. The woman and her child had not left the district in which they lived for some days, and, as a result of this, I refused to make the diagnosis malaria eclamptica, because this region is one of the most healthy in the city. Nevertheless, on account of the gravity of the case and the high temperature (rectum, 40.5°), I gave an injection into the buttock of 0.25 quinin mur. and ether, and at the same time ordered an aperient clyster and sinapisms to different parts of the body. An hour later the temperature had sunk to 38° and consciousness had returned.

The following morning I administered another injection of 0.25 quinin mur. The paroxysm did not occur.

A month later, in September, a new convulsive attack with fever, but milder than the first, occurred. Injection of 0.25 quinin. The paroxysm was not repeated. Since then the child has manifested no symptoms of recurrence.

Latent malaria has likewise been observed in very young children. Whether it is as frequent as Benoît assumes must remain for the present questionable. Kingsley also claims that he frequently saw latent malaria in the form of periodic headache, cardialgia, tonsillitis, laryngitis, convulsive cough, etc. Bohn has described, in a masterly way, cases of periodic torticollis, neuralgias of the trigeminal, sciatic, and hemorrhoidal nerves, as well as cardialgias, intermittent vertigos, and psychopathies. Especially interesting is his description of a frontal neuralgia in a boy one and a half years old. Hemorrhagic diarrheas of quotidian and tertian type, with little or no fever, have been likewise described by Bohn as latent malarias. Kroner observed a frontal neuralgia, quartan in type, in a seven and a half year old girl. Old people are no more spared than other classes.

The paroxysms produced by parasites of the first group differ in no way from those in younger people. Infections with parasites of the second group run a different course only inasmuch as the symptoms, especially the fever, are much less conspicuous. On this account the disease may be apparently unimportant, and manifest itself in somnolence, slight stupor, and malaise, while in reality the danger may be imminent. The termination in these cases usually occurs after a sudden short coma. This behavior is similar to that seen in other infections (pneumonia, influenza, etc.).

RELAPSES; REINFECTIONS.

Malaria is one of those infectious diseases in which a relapse may be considered an essential feature. In this respect it resembles most closely acute articular rheumatism. It is a daily observation to see a man who has passed through a series of malarial paroxysms, one, two, three, or more weeks later manifest one or several paroxysms, and it makes little difference whether the first disease recovered spontaneously or was cured by the action of quinin. This may be repeated several times, and we frequently see persons who have acquired their primary infection in summer or autumn tormented the whole winter, even to the subsequent spring, by occasionally recurring paroxysms. The appreciation of this inclination was the origin of the therapeutic procedure of combating the anticipated relapse by a few doses of quinin, which are ordinarily administered two or three weeks after the last paroxysm.

We wish expressly to insist that we mean by relapse the reawakening of the disease-symptoms by parasites that have remained in the organism from an earlier period. These relapses must be sharply separated from reinfections—that is, new infections of the organism after it was free of parasites.

It is clear that in concrete cases this is not always possible. When we have to do with people who continue to reside in a malarial region after a previous attack, we are naturally often unable, by our present methods, to determine whether the new fever has been caused by the old parasites in the mean while latent, or by a reinfection, for which there is ample opportunity. This separation can be made with certainty only when the blood examination in the second case shows a species of parasite different from that which occurred in the first, in which case it is evident that we have to do with a reinfection.

It is also quite as clear when a person who was infected in a malarial region suffers later from repeated attacks in a locality free from malaria. In this case we have to do naturally with a positive relapse. There are even sufficient grounds for the diagnosis of a relapse when a person confined to a well-located hospital manifests new fever paroxysms.

Relapses are seen in cases of fever of the first as well as of the second group, though in the latter they are more frequent and obstinate. Among the first group quartan relapses occur more frequently than tertian.

For a long time no effort has been spared to find a rule for the occurrence of relapses.

Werlhof claims to have found that tertian fever usually recurs in the second, quartan in the third, week, and on those days on which a paroxysm would have occurred if there had been an uninterrupted continuance of the fever.

Barudel drew, from the investigation of a large amount of material, that quotidian fever relapsed most commonly on the seventh day, tertian on the fourteenth, quartan on the twentieth.

According to Borius, relapses occur preferably on the seventh, fourteenth, twenty-first, and twenty-eighth days. Among 226 cases observed in Sénégal, 128 had regular relapses, and of these, 18 on the seventh, 64 on the fourteenth, 31 on the twenty-first, 9 on the twenty-eighth day. Ninety-eight cases relapsed differently (ninth, tenth, sixteenth, twentieth day). Borius remarks that all these people took quinin in the interval, and he is convinced that the relapses, in the majority of cases, occurred on account of stopping it.

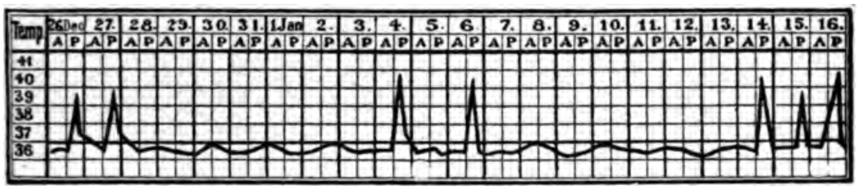

FIG. 37.—RELAPSE OF SEPTAN TYPE (after Livio Vincenzi).

Dudon observed in the quotidian fevers of the east coast of Africa that relapses occurred almost regularly on the seventh day. As a matter of curiosity, we add that a few decads ago (even to-day by some physicians) relapses were associated with the phases of the moon. Experience has shown that these rules do not apply to a large number of cases—in other words, the exceptions are more frequent than the regular types.

It sometimes happens that several relapses follow one another at regular intervals—for instance, relapses have been occasionally observed showing one or several paroxysms, every seven or eight days, and the interval may be longer, even to a month. Livio Vincenzi, who has devoted considerable attention to relapses, saw several cases with intervals of seven days. Fig. 37 has been taken from his publication. This case was a woman who was attacked by quotidian fever in October, with a relapse in December. The curve in the figure shows that two further relapses followed, with seven days' interval. The blood examination discovered small ameboid parasites without crescents. At the time of the apyrexia parasites were missed from the blood for several days at a time.

With such regularity in the relapse there is an inclination to assume that we have to do with a type standing in a genetic relation to the evolution of the parasites. This was the conclusion of the older writers when they spoke of septan, octan, monthly, etc., types. Even Golgi considered them as types associated with the life-cycle of special parasites, and designated then as "Febbri malariche a lunghi intervalli." Yet when we consider that this regularity is only exceptional, that in the same case the relapses occur after longer and shorter intervals, that the blood examination, especially from the spleen, shows parasites with a life-cycle of from twenty-four to forty-eight hours, we must repudiate this idea and speak not of fevers with long intervals, but of relapses. Moreover, on ceasing the administration of quinin, we see these fevers with long intervals change to tertian or quotidian (Bestion). Borius, for instance, mentions that his cases, which relapsed on the twenty-first day, were given quinin as a prophylactic on the seventh and fourteenth. We repeat, therefore, again that we are not justified in speaking of fevers with long intervals, or fevers of septan type, since they are only relapses. The general experience is that relapses occur in the beginning in shorter, later in gradually lengthening, intervals.

There are frequent statements of malarial fever relapsing after years; yet so far as I have gone into the literature I have found no case in which this was determined with the necessary certainty. In my opinion only the examination of the blood, together with a critical consideration of all external factors (especially the epidemiologic conditions), could decide such a case. I must confess that to me such an occurrence appears very doubtful. We are naturally not justified in stamping a fever as a malarial relapse simply because the person affected suffered some years before from malaria, even when the objective examination shows for the moment no other intelligent cause. It is only necessary to recall how frequently we see feverish infections to which we can give no name. A positive blood-finding alone can exclude reinfection.

The type of the relapse is most frequently intermittent, sometimes subcontinued. Even cases which began as severe continued or subcontinued often manifest in the relapse simple quotidian, tertian, or irregular intermittent fever. The relapse consists sometimes of one single paroxysm; again of several consecutive ones. With successive relapses from the same case the type may change.

The other symptoms are usually less severe than in the primary disease, yet severe relapses do occur and it is not rare to find them showing the same pernicious symptoms as the original disease, or even others.

During the relapse the blood examination is always positive. All species of parasites may be found, and even several varieties simultaneously. Parasites of the second group are the most frequent.

During the apyretic interval a few ameboid parasites, isolated melaniferous leukocytes, often a considerable number of crescents, are usually found in the peripheral blood, though the blood examination may be absolutely negative for days.

Frequently some psychic or physical circumstance appears to be responsible for the outbreak of a relapse, as pleasurable and intellectual excitement, change of residence, the performance of some unaccustomed work, Bacchanalian or venereal excesses, colds, dreams, indigestion, etc.

Reinfection is very common. Different from so many other infectious diseases which induce a certain amount of immunity, malaria seems rather to increase the predisposition to a new infection. Although certain races show less susceptibility than Europeans (for instance, the negroes), this seems to depend more on a congenitally low predisposition than on an acquired immunity.

The reinfection may be caused by the same parasites as the first infection or by others.

CHRONIC MALARIAL INFECTION.

By chronic malarial infection we understand one continuing for months. This continuance does not depend on reinfection, but on an obstinate persistence of the virus. From one point of view malarial infections may be divided into acute and chronic, depending on whether the infection ceases in a short or continues for a long time, yet this division lacks a rational and sharply cut basis, and we have, consequently, made use of the etiologic classification. Still, practical reasons demand that malarial infections be considered for a moment from this standpoint, in order to call attention to certain elements which might otherwise escape observation.

Inasmuch as cases with one or several relapses are more frequent than those which cease after a shorter or longer series of paroxysms, we might say that the majority of malarial infections show a chronic character. Yet to designate as chronic every case which showed within two to four weeks a relapse would be of no practical value; therefore we must insist that the symptoms of the infection continue for months.

Without specific therapy, the great majority of malarial cases would be chronic in this latter sense, though with it the cases are limited to a relatively small number. The malarial infections caused by the first group of parasites are comparatively seldom chronic, especially when rational treatment and the proper hygienic measures have been employed, yet sometimes, in spite of proper treatment, good nourishment, healthful dwelling-place, etc., they relapse for months and months—in other words, become chronic. This is true of quartan much more frequently than of tertian fever.

The parasites of the second group constitute the principal contingent in chronic infections. The resistance shown by certain developmental phases of these parasites to quinin, on account of which the infection becomes chronic, will be discussed in the sections on Pathogenesis and Therapy.

Though we usually succeed, by means of quinin and proper sanitary regulations, in preventing a relapse, we frequently fail to get rid of all the organisms. In this guerrilla warfare the therapy is unable to reach the enemy intrenched in the parenchymatous organs, though it is usually successful when the troops come out into the open field of the blood-vessels. It is, therefore, evident that chronic cases are much more frequent in malarial regions where parasites of the second group are endemic than in localities where only parasites of the first group exist.

The parasites of the second group become active in the summer and autumn months. From these months, therefore, date the majority of chronic infections. The patient—supposing the case to be a soldier in a colony infected with malaria—is, for instance, in August, brought to the hospital on account of a typhoid subcontinued. After eight to ten days he is convalescent, though still very pale, anemic, weak, nervous, and showing a splenic tumor. He recuperates quickly and is about to leave the hospital, when, on the last day, he manifests a severe paroxysm. The paroxysms then repeat themselves, following a tertian type, until interrupted by quinin. The patient is again anemic, the splenic tumor somewhat enlarged, etc. Recuperation now requires a longer time, and has probably not progressed very far when another relapse occurs, and so until late in the winter; more than that, we sometimes find the patient still in the hospital the subsequent spring. He is eventually given permission to return home. He arrives at home in a pitiable condition; his relatives remark the "burnt-up" appearance, which is nothing else than the ashy melanosis of a chronic malaria. He gradually gains strength and considers himself almost entirely well, when one day an outbreak of blackwater fever occurs, or he falls into a comatose condition which gives the physician much difficulty in the diagnosis. The patient may succumb to this attack, or he may recover and remain entirely well, without symptoms of malaria, for the remainder of his life. In this fashion or similarly run the majority of cases which we have in mind.

In order to diagnose chronic malaria the following clinical symptoms must be present: 1. Occasionally recurring paroxysms of malaria for months (relapses); these may be normal or latent. 2. A certain degree of anemia. 3. Enlargement of the spleen and eventually enlargement of the liver. 4. The same species of parasites in the blood throughout the whole period. 5. General characteristic appearance.

In regard to the relapses, we have little to add to what has been said in the previous section. They are frequently only suggested, manifest no chill, and the patients often have no knowledge of the fact that they are passing through a fever. Moreover, people with chronic malaria are frequently so little sensitive to elevations of temperature that they fail to remark even high ones. Patients presenting all the symptoms of chronic infections sometimes absolutely assert that they have never suffered from fever. Such assertions are to be regarded with the greatest skepticism, and from my own frequent experiences are to be credited only when the temperature was taken regularly. The relapse may be latent—in fact, it is especially in chronic malaria that this manifestation occurs. Finally it must not be forgotten that the relapse may be pernicious, and that it is the chronic infection which oftenest gives rise to pernicious symptoms (for further details see Catrin).

The anemia may be of varying intensity or even entirely wanting. This last happens when the relapses take place at long intervals from one another, when during the relapses there is no great destruction of red blood-corpuscles, and when the blood-making organs possess a productive power capable of covering the loss in a short time. As a rule, only mild grades of anemia are seen in cases of chronic infection with parasites of the first group.

Still we usually find an outspoken chloranemia—*i. e.*, a diminution in the hemoglobin and in the number of erythrocytes, the decrease in the former being disproportionately great in comparison with the latter. The red blood-corpuscles vary in size, microcytes being most frequent. A slight poikilocytosis may also occur, and isolated nucleated normoblasts may be found.

The leukocytes are regularly diminished in number, both relatively and absolutely. Kelsch and Kiener found in 33 cases of chronic malaria the proportion of the red to the white blood-corpuscles constantly altered in favor of the former. This fluctuated between 1:800 to 1:2000, yet with a relapse or an acute complication leukocytosis usually occurs.

Enlargement of the spleen is rarely absent, and the more frequent the relapse, the larger it becomes. The organ frequently extends several finger-breadths beyond the border of the ribs. Its consistence is moderately firm. It is often the seat of spontaneous pain, sometimes of a lancinating, again of a dull, pressing or constricting character. The pain may radiate to the spinal column. The spleen is frequently sensitive to pressure. According to Duboué (de Pau), when an enlargement to percussion is not evident, the spontaneous pain will indicate the existence of malaria, though in our opinion too great weight should not be placed on this circumstance. The splenic tumor usually increases in volume during a relapse and no longer returns to normal during the interval.

The liver is likewise frequently enlarged, though this is always more difficult to determine, especially when the patient was unknown to the examiner previously. It is generally recognized that this organ may show quite well-marked differences in size in response to physiologic conditions. An extension beyond the border of the ribs two or three finger-breadths may in one case indicate an enlargement, in another, be physiologic. It may also be painful and manifest subjective disturbances similar to those in the spleen.

The blood examination during the relapse, as well as immediately before and after, is always positive. During the intervals there may be no trace of a parasite in the peripheral blood, or only organisms of the crescentic order and melaniferous leukocytes.

Occasionally in the intervals, as especially Vincenzi has shown, ameboid forms, even in the act of sporulation, are observed. The fact that no fever symptoms are manifested may be due to a certain habituation of the organism or the vasomotor centers.

The parasites may be of one species, when they usually belong to the second group, or may be of different species—most commonly a mixture of ordinary tertian parasites with parasites of the second group.

The finding of parasites is essential to the diagnosis of a relapse, since chronic malaria, as well as malarial cachexia, shows conditions associated with fever that are not dependent on the malarial infection. We will discuss these conditions later on.

The general appearance depends in great part on the degree of anemia and hydremia.

The skin is usually tawny, not only in places exposed to the sun, but over the whole body. This peculiar color is made up of pallor and pigmentation, to which is often added a slight icterus, and is encountered at every step among the inhabitants of malarial regions. Occasionally a more intense degree of melanosis of the skin is observed. In contrast to this, however, there are cases with only a slight pallor of the lips, and even this may be wanting if no relapse has occurred for a long time and the blood has had time to recuperate.

Edema not rarely accompanies the hydremia. In this stage of the disease it is usually slight, confined to the legs, and transient in contrast to the edema occurring during the cachexia.

Corresponding to the severity of the anemia the pulse is frequently hastened. After physical effort, palpitation, a feeling of oppression, and dyspnea often occur just as in anemic persons generally.

Kelsch and Kiener maintain that, in addition to the anemia, the hyperemia of the spleen and of the liver and the increase in function of these organs (the removal of the pigment) throw extra work on the heart. In 80 autopsies of chronic malaria they found more or less hypertrophy of the heart 34 times. As a rule, this was slight and limited to the left ventricle. Even during life the hypertrophy of the heart is not rarely perceptible in a stronger impulse (Julié).

Bronchitic disturbances are frequent. They sometimes disappear with the relapse, but again obstinately persist, when they may lead to capillary bronchitis or pneumonia.

The digestive tract is not regularly affected, yet patients often complain of general disturbances, like sensations of pressure and constriction after meals, an inclination to constipation, diarrhea, pyrosis, etc.

In addition patients complain frequently of malaise, headache, vertigo, and sleeplessness. Their voice shows alterations; they become ambitionless, surly, and peevish.

In the absence of complications, the urine contains no abnormal constituents, though frequently urea and urobilin are increased (Kelsch and Kiener).

Chronic malaria may be cured. This is best accomplished by a change of residence to a healthy climate, though this is not a guarantee of eventual cure. There are many cases of relapses—even pernicious relapses with fatal terminations in salubrious regions, for it must not be forgotten that the patient carries the parasite with him.

MALARIAL CACHEXIA.

The term malarial cachexia is given different meanings by different writers. Some understand by it a condition of the organism, the principal characteristic of which consists in the impossibility of eliminating the injurious influences put into play by the malarial infection. This impossibility being final, the organism is doomed to destruction. Others make the definition broader and include certain transitory disturbances. The former take certain anatomic, irremediable alterations in the tissues as the basis of the cachexia; the latter, either persistent or transitory disturbances, due to functional as well as pathologico-anatomic processes. A common bond between both definitions is made by the similarity of the clinical symptoms. It is only in their prognosis that they are diametrically opposed, in that in one case it is absolutely unfavorable; in the other, only dubious.

Since we are discussing malaria principally from its clinical aspect, and are looking to the requirements of the physician, we will pay no further attention to the former definition, but will include under our term every condition characterized by a persistent or transitory loss of power on the part of the tissues coming into consideration, namely, the bone-marrow, liver, and spleen.

We would understand the pathogenesis very inadequately if we were to attribute these disturbances, even principally, to the processes in the blood.

The red blood-corpuscles are the first to meet the attack of the malarial parasites. These are destroyed by billions and billions, but it is the blood-making organs that must make good this loss. Moreover, this is only half of what they must do, for theirs is the work of removing the débris of the hemoglobin consumed by the parasites (the melanin). This work falls principally on the liver, but also on the spleen, the lymph-glands, the kidneys, and the intestinal mucous membrane. As long as the bone-marrow and these organs are equal to the demands made by the organism on account of this devastation of the parasites, so long will there be no question of cachexia; but as soon as a disturbance of activity occurs in these organs, whether this is only functional and, therefore, temporary, or organic, and in this case unalterable, there arises the condition which we call cachexia.

Kelsch and Kiener very appropriately compare the condition of the organism in the course of a malaria to that of the heart during a valvular affection. So long as the reserve power and the hypertrophy of the heart muscle are sufficient to compensate for the disturbance, so long the organism shows none at all or only slight symptoms of the valvular disease, but as soon as the activity of the heart is interfered with, all kinds of compensatory disturbances occur. In the same way in malarial infection when the tissues in consideration become functionally insufficient, the symptoms of cachexia appear.

From this it is evident that the cachexia consists principally of the anemic and hydremic symptoms, associated with those due to overloading of the organism with pigment. Since the functions of the organism are depressed and no rapid compensation is possible, we find grouped about these other symptoms of the most varied kind.

Considering the number of disturbances that anemia and hydremia alone may produce; recalling the lessened resisting power of an organism paralyzed in its most important functions to different injuries; remembering that the malarial pigment when it cannot be removed by way of the bile and of the urine remains lying in the parenchyma as an irritating foreign body, and adding to this that, in the majority of cases of cachexia, the malarial parasites are still capable of continuing their depredations on the erythrocytes and of producing toxin, we must realize the endless perspective of symptoms that can arise in malarial cachexia.

Cachexia occurs most frequently in individuals exposed uninterruptedly for years to the influence of the malarial virus. It is, therefore, most common among the inhabitants of severe malarial regions. Moreover, it is almost always the poor and miserable, who live under bad hygienic conditions, that become its victims. They draw in, as it were, the malarial poison with their mother's milk, spend their youth in the midst of the pest, and get no opportunity to change their residence so as to recuperate. Cachexia is seldom seen in immigrants, first, because they are usually at an age when the organism is more resistant; secondly, and this is the principal reason, because the strangers are usually in a position to seek, at least now and then, a more salubrious climate in which to recuperate. In malarial regions soldiers in garrisons are commonly returned home after a series of malarial paroxysms, and office-holders and merchants confine their stay to the shortest possible time.

Some cachectics assert that they have never suffered from fever, though I put little faith in these statements. We have mentioned in several places how frequently patients are unconscious of the fever, and when this is the case in well-educated men accustomed to observe themselves, how much more would it be so in people who, in their arduous struggle for existence, find little time to devote to general health. Léon Colin, together with Nepple, Bailly, Monfalcon, Boudin, Catteloup, and others, claims that cachexia does occur in the natives without preceding fever, and he refers to the cachexia of lead-poisoning, which sometimes sets in without colic, paralysis, arthropathy, etc., as an analogy.

In the majority of cases the cachexia is preceded by numerous infections or relapses and so develops gradually. We speak of such a cachexia as chronic.

Sometimes the symptoms come on rapidly at the close or in the course of an infection; in this case we speak of acute or galloping cachexia. It is very rare to see the acute cachexia set in after a single infection (cases of Jacquot, L. Colin).

Acute cachexia occurs almost only in severe malarial regions, as Sénégal, Guadeloupe, the west coast of Africa, Madagascar, India, and Tongking. A few cases have been observed in Holland and in Italy.

Roux is of the opinion that the constitution of the patient and the hygienic conditions under which he lives exercise the greatest influence on the rapidity with which the cachexia develops. He believes that the intensity of the attack has nothing to do with it. Moreover, Haspel and Kelsch and Kiener stated previously that acute cachexia usually occurred in individuals weakened by hardship or excesses. Still, exceptional cases have been seen in persons who were, previous to the attack, apparently strong and healthy.

The statement that the severity of the attack is of no importance in the production of the cachexia strikes me as questionable. Generally speaking, it is very difficult to make a criterion for severity. Yet it cannot be denied that it is usually the estivo-autumnal fevers that lead to cachexia. The cases consequently occur in greatest numbers during autumn and winter. Though the parasites of the second group are the principal causal agents, those of the first group sometimes play the rôle. This is especially true in case of obstinately relapsing quartan fever.

The question at issue has not yet been sufficiently investigated to speak conclusively about it. Researches in regard to the etiology of cachexia from a parasitic point of view are, therefore, desirable.

The **symptoms** of cachexia are as follows:

Anemia.—This is a very special characteristic. To it is owing the color of the skin, which often shows an excessive degree of pallor, in spite of the brownish discoloration contributed by the melanosis and a frequently associated light yellow. It explains, too, a series of subjective symptoms, as vertigo, ringing in the ears, malaise, disinclination for work, headache. It may be made responsible for the diminution in intellectual activity, the languid mumbling or indifferent voice, the sleeplessness.

Further attributable to the anemia are some of the vascular symptoms, as dilatation of the heart, tachycardia, accidental systolic murmurs, venous murmurs, etc.; likewise the dyspnea associated with any physical exertion.

Finally, we place at its door the cold sensations, the cold skin, and the subnormal temperature, which fluctuates usually under 37°.

The blood examination shows the number of red blood-corpuscles to be greatly decreased—often under 1,000,000.

The *leukocytes* are sometimes diminished in number, though again there is a pronounced leukocytosis. L. Colin found, among 65 cases, a more or less considerable increase in leukocytes in 50, while Ascoli claims a striking leukopenia.

The *hydremia* constitutes the second cardinal symptom. There are no actual specific gravity estimations, yet the very low hemoglobin percentage, the hypalbuminosis, as demonstrated by Castan, Léonard, and Foley, and the edema leave no doubt as to its existence.

Edema as a direct result of the hydremia is never entirely wanting and is usually marked. Contrary to the conclusions of Cohnheim and Lichtheim, it has been experimentally proved by Stricker and Gärtner that edema may be produced by hydremia.

In regard to its distribution, the edema shows the same character as that of nephritis. The pale face is frequently bloated; the eyelids are swollen, and swellings are also encountered on the extremities and other situations of the body. Effusions into the serous cavities, like ascites, hydrothorax, hydropericardium, are frequent. Symptoms pointing to edema of the brain are sometimes observed, and edema of the glottis or of the lungs may become actually threatening. Still, not every edema in the course of a malaria is to be regarded as an expression of cachexia. This is even less true than that an anemia or a splenic tumor should make a cachexia. It is not rare to see a more or less marked edema follow a series of paroxysms and disappear within a few days after the cessation of the fever. I have observed this especially in children, though occasionally in adults.

In the second place, edema and transudates may occur and be attributable not to the hydremia, but to other causes, like local stasis, inflammation, and nephritis.

In this regard we may call attention to the stasis edema of venous thromboses which are the result of the deteriorated condition of the blood. From experience we know that under the influence of edema and hydremia, as in severe chlorosis, leukemia, the cachexia of carcinoma, etc., the blood has a tendency to coagulate in the vessels, with the production of thrombi. This same tendency also exists in malarial cachexia. These thrombi may form in any part of the vascular system, the heart itself, as well as peripheral veins, the portal vein, etc. The dangers which they give rise to are beyond our scope, though we may see that sometimes, as a result of arterial thrombi, more frequently of emboli, gangrene of the extremities occurs as a complication.

Among the other symptoms produced, at least in part, by the deteriorated condition of the blood, are frequent *hemorrhages*. Epistaxis may be a daily occurrence, and not infrequently we see larger or smaller hemorrhages into the skin, hemorrhages from the gums, into the muscles, from the bladder, from the female genitals, into the serous membranes, into the brain, into the spleen and liver, into the retina, in the form of hemoptysis, hematemesis, etc. The thought of scorbutus frequently arises, and undoubtedly it often occurs as a mixed infection—but about this later. Intermittent hemorrhages have been reported (Verneuil), though on scarcely sufficient evidence. It has also been asserted that slight wounds, like the sting of insects, the bite of leeches, give rise to severe hemorrhages, but this is not generally true. Operations on cachectics usually proceed without marked loss of blood (MacNamara, Duka).

The hemorrhages naturally may have a local cause; the hematemesis, for instance, may be the result of thrombosis of the portal vein or of cirrhosis of the liver; hemorrhage from the left nasal cavity, the result of splenic tumor, etc. It has sometimes been affirmed that after such a hemorrhage the spleen diminishes in size.

The overloading of the organs with *pigment* expresses itself in melanosis of the skin, which is more intense the shorter the time since the last paroxysms. It may reach such a degree that the skin becomes of a bronze color.

The *splenic tumor* is much more important. It grows, as a rule, in the direction of the umbilicus, more rarely taking a cross position when it lies in the epigastrium. The tumor may extend into the small pelvis and meet its first resistance on the pelvic bones. In this case it manifests no respiratory displacement. It usually produces a feeling of weight in the left half of the abdomen, of which patients frequently complain. It is sometimes the seat of stabbing pain, the result of an intercostal neuralgia or perisplenitis.

According to Laveran, the spleen reaches this immense size only in cases not at all or insufficiently treated with quinin during the acute infection.

Not so frequent as the splenic tumor, yet occurring in a large percentage of cases, is a *tumor of the liver*. M. E. Colin found, in 61 autopsies, the liver normal in size 18 times, enlarged, 43 times. It is sometimes relatively more enlarged than the spleen.

Occasionally, instead of enlarged, it is decreased in size, apart from any cirrhosis. This is due to simple atrophy of the organ. In addition to these cardinal symptoms there are others which demand a short description.

In every severe case of cachexia the parenchymatous organs suffer tissue changes, with the production of corresponding symptoms. We may mention especially secondary diseases of the liver, as perihepatitis, hypertrophic biliary cirrhosis, atrophic cirrhosis, cholangitis, etc.

Fever may be entirely absent, and the elevations of temperature which we see from time to time in many cases are usually due to relapses or complications.

The relapses commonly show an intermittent character. They manifest, as a rule, no severe symptoms and no marked elevations of temperature, though there are exceptions, and a relapse may be pernicious and the patient succumb.

They usually occur at long, frequently irregular intervals. The cold stage is but little pronounced or absent. The elevation of temperature usually remains within moderate limits. The sweating is not profuse, though it continues for a long time. Among the dangerous forms L. Colin mentions algid, syncopal, icteric, comatose, apoplectic, subcontinued autumnal pernicious as the most frequent.

The parasitologic investigations in cases of cachexia are as yet too few to judge of a relationship. In a certain number of cases the parasitic infection is undoubtedly continuous. Isolated parasites, especially of the crescent class, are frequently found in the blood, even though not at all times. During a relapse the parasites are quite as numerous as in recent infections. Whether there are cachectics whose organs are entirely free from parasites must be regarded as an open question. *A priori* this does not seem impossible—in fact, it seems to a certain degree probable.

In addition to the paroxysms of fever the result of relapses we see feverish conditions that cannot be regarded as due to the malarial infection, on account of their behavior to quinin. Moreover, frequently no local disease can be found, and we are obliged to speak of symptomatic fever. Undoubtedly a great part of these fevers are dependent on organic anatomic processes, as, for instance, the connective-tissue formations in the liver and spleen, the phlebitides, thrombi formations, etc.

The *mouth* is frequently the seat of gangrene, the gums especially showing an inclination to necrosis. From there the gangrene not rarely spreads to the lips and cheeks. The jaw bones are laid bare. Gangrene of the soft palate and of the tonsils at the close of apparently mild anginas is frequently observed.

The *gastro-intestinal tract* is regularly the seat of symptoms, even though these are not characteristic. Loss of appetite, a feeling of compression in the stomach after meals, an inclination to constipation, more seldom to diarrhea, are common symptoms. Dudon frequently observed attacks of intense colic (colique sèche) associated with contracted or tympanitic abdomen.

Catarrh of the respiratory tract is very common. This may become dangerous by extension to the fine bronchioles, by the production of bronchopneumonia, etc. When this last occurs, it not rarely terminates in gangrene.

The *nervous system* likewise participates, as mentioned under anemia and hydremia. In addition to the symptoms considered there, we see attacks of vertigo, fainting, paralysis of the bladder, a trembling gait, and trembling of the hands or of the whole body. Laveran saw this last disappear on the administration of quinin.

According to Mouneret, hemeralopia is not infrequent. Sulzer observed chronic optic neuritis, melanosis of the papilla, retinal hemorrhages, and changes in the vitreous humor.

Gangrenous processes of the severest kind may occur about the genito-urinary apparatus. Gangrene of the penis, especially in association with chancre, and gangrene of the labia, extending to the mons veneris, the thigh, or the perineum, is not infrequent.

The *urine* is usually increased, but may be diminished in quantity. It frequently contains urobilin. When nephritis or amyloid disease complicates, it is rich in albumin. Hemoglobinuria and hematuria are not rare.

The *mixed infections* to which the unresisting organism of the cachectic readily succumbs are many. We will devote more space to them in the section on Complications, and will mention here only the most frequent and, therefore, the most characteristic: Scorbutus, gangrene, pneumonia, cirrhosis of the liver, nephritis, phlegmon, to which we may add, as a sequela, amyloid degeneration.

The general nutrition of the cachectic is bad, even though the bloated face, the edema of the legs over the emaciated muscles, conceals more or less the disappearance of the fat. Gaylor characteristically describes the general impression of the cachectic in the words, "Tumidi ventres, lienosi, inflatis cruribus, flavo viridive colore exsangues."

Cachectics always look much older than they are. Even cachectic children have somewhat of an aged appearance; still more so, cachectics in middle life.

Cachexia in Children.—The organism of the child succumbs to cachexia even more readily than that of the adult. It is not rare to see children manifest a general dropsy after a few paroxysms. On frequent recurrence of the attacks the general picture of cachexia develops as in adults. In relation to this Bohn says*: "In malarial cachexia the subcutaneous fat eventually disappears, the muscles become thin, flabby, and powerless, the skin whitish-yellow, grayish-green, or grayish-brown, and, as a special characteristic, an immense splenic tumor develops. Spleens from 22 to 24 cm. long and 6 to 11 cm. broad, reaching obliquely to the umbilicus or perpendicularly into the iliac fossa and to the pubic bone, are not uncommon. Sometimes the hypertrophic organ grows more upward or in breadth and interferes with respiration. In contrast to the general emaciation the abdomen is irregularly enlarged, either throughout or in its left half. These chronic splenic tumors are always tender on pressure and sometimes spontaneously painful. They occasionally interfere with the movement of the left leg, and in a six-year-old boy produced eccentric pains in it. Chronic intestinal catarrh is scarcely ever absent. The petechiæ and purpura that sometimes cover the whole body are likewise to be attributed to the cachexia.

The **course and duration** manifest striking differences. Acute cachexia ordinarily runs a more rapid course, especially when accompanied by gangrene, hemorrhages, etc. Chronic cachexia extends over months and years, yet a pernicious attack or one of the previously named severe complications may at any time prove fatal.

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* *Loc. cit.*, p. 123.

Mild cases of cachexia usually end in recovery. This is complete only when the parenchymatous organs have suffered no structural changes, making compensation impossible. Cases with advanced disease, especially of the liver, spleen, and kidneys, offer a bad prognosis. Such people may escape their fate for years, become even capable of doing light work, yet the danger continually hangs over them of falling a victim to a relatively mild intercurrent affection. To them is applicable Doni's description of the home-coming reapers: "Horum plerosque videas morbosos, pallidosque aspectu, ac vix firmatis vestigiis catervatim moestos ingredi, quippe æorum magna pars in urbanis nosocomiis vel vitam relinquunt, vel longo tempore cum morte luctantur."

The end may occur under the most different intercurrent affections, among which certain secondary affections of the liver, like hypertrophic cirrhosis, cholangitis, atrophic cirrhosis, simple atrophy, play a prominent rôle. These produce death under feverish and cholemic symptoms, with or without icterus. Trousseau and Duclos (de Tours) state that, at a certain stage, a progressive continued fever, with marked increase in the pulse-rate, ordinarily breaks out, which leads to a fatal termination in days or weeks. Death in these cases usually occurs under coma.

The general syndromes presented by cachectics show many similarities, yet there are certain differences which are sufficiently pronounced to make a division of cachexia in several forms justifiable.

In the introduction we distinguished an acute and a chronic cachexia. This differentiation is not limited to the greater or less rapidity with which the cachexia develops, but is evident, too, in certain characteristic symptoms.

Acute cachexia is characterized by the predominance of hydremic, hemorrhagic, and nutritive disturbances, to which mixed infections that show a striking tendency to gangrene are frequently added. The picture is dominated by a rapidly occurring general dropsy, hemorrhages from different regions, phlegmons, abscesses, gangrenous processes, and decubitus.

We mentioned before that this form of cachexia affects especially badly nourished, worn-out individuals. Kelsch and Kiener describe it under the name "cachéxie hydroémique, et gangrène," and I consider it an error when French writers identify Haspel's "fièvre putride scorbutique épidémique" with acute malarial cachexia. In my opinion, Haspel's observations were applied to epidemics of scorbutus which carried off advanced cachectics, as well as individuals whose nutrition and resisting power had been lessened by some other preceding disease. After every effort to attribute the scorbutic affection to a similar etiology as malaria, Haspel himself writes*: "Cette maladie ne passait pas toujours par les phases de la fièvre intermittente, ou la vit se déclarer dans les salles, chex les convalescents de diverses maladies." Moreover, we find, among his three anamneses, no case with dropsy and only one with a moderately sized splenic tumor.

Chronic cachexia is much more frequent. Its course is monotonous in comparison with that of acute cachexia. Edema, enlargement of the liver and spleen, different disturbances due to anemia, feverish or latent relapses, constitute the principal symptoms, while hemorrhagic, septicemic, and other complications occur only occasionally.

Kelsch and Kiener, to whom we owe the most thorough investigation of this question, have endeavored to divide chronic cachexia into subclasses. They differentiate: 1. Chronic cachexia the result of the overloading of the parenchymatous organs, especially the liver, with pigment (siderosis, "Surcharge ferrugineuse du foie"). 2. Chronic cachexia with general atrophy of the organs, especially the liver. 3. Amyloid degeneration.

While recognizing all that we owe to the splendid work of these two French investigators, we cannot regard this classification as final and objectionless. Without entering into a deep discussion, we may remark that this classification lacks a common factor. In form 1 the overloading of the parenchymatous organs with pigment is made the point of differentiation, and we would, therefore, logically conclude that in form 2 no siderosis was present. Yet this is not the case. Quantitative distinctions that may be slight can scarcely be taken as criteria on which to base a classification.

In regard to the amyloid degeneration, this can be made a criterion for the classification of malaria, no more than of tuberculous cachexia, since it is rather to be looked on as a sequela.

In spite of these defects Kelsch and Kiener are to be congratulated on their endeavor to classify cachexias, and in further researches this classification may be accepted as a basis.

The clinical symptoms of these three forms show the greatest similarity, though in form 2 the rapidly developing ascites, the result of occlusion of the portal circulation by spleen-cells, may show also a great similarity with atrophic cirrhosis of the liver. Still there is usually wanting in neither form 1 nor 2 more or less developed cirrhotic changes in the liver, about which we shall say more in the sections on Complications and Sequelæ and Anatomy.

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* *Loc. cit.*, p. 403.

[NOTE.—The recent discovery, by Leishman, of a new parasite in the blood obtained by splenic puncture from cases of so-called "malarial cachexia and enlarged spleen," of common occurrence in India, necessitates a complete revision of the nomenclature and pathology of these cases. This parasite is also found in that large mass of cases called in India kala-azar, kala-dukh, or also tropical splenomegaly or cachexial fever. The parasites, which are characterized by the possession of a large and a small nucleus, resembling those of a trypanosome, appear to be entirely intracellular, occurring mainly in large mononuclear and endothelial cells. Identical parasites also occur in "Delhi boil" or "tropical sore." They undoubtedly play a large part in the pathology of Indian fevers. It has been shown by Rogers that these parasites have a flagellate stage.—ED.]

COMPLICATIONS AND SEQUELÆ.

In the course of acute and chronic malaria, and even more so in the course of cachexia, complications are frequent, and while they show a certain genetic relationship to the disease, they are usually not directly dependent on it. Some of these complications occur so frequently that they seem to deserve special description. This description is, moreover, justified, since not infrequently, under the influence of the malaria or its results, the complications assume a different form from that seen under other circumstances.

These complications are in great part the result of mixed infections, though a large number, too, depend on chronic inflammatory processes due chiefly to the overloading of the organism with pigment. A smaller number are the effect of degenerative processes, and finally some are of a purely mechanic nature.

We consider it most advisable to describe these complications in connection with the systems of organs which ordinarily manifest them.

Among the organs that participate most frequently we may mention, first, the respiratory tract.

RESPIRATORY TRACT.

In the course of previous remarks we have repeatedly alluded to the frequent affections of the bronchi in malaria. Here we need recall only the common symptoms, dry cough, dyspnea, and subcrepitant râles, that occur in the course of an acute intermittent and the chronic bronchial catarrh of cachectics.

The pulmonary complications vary in frequency with race and local conditions. Fayrer states that they are frequent among the natives in India; Partridge and F. Plehn, the same in Assam and in West Africa; Triantaphyllides found bronchitis in 7 per cent. of the cases in Batum.

The *bronchitic symptoms* of acute malaria are usually only slight, and continue for only a few hours after the paroxysm, or cease with it.

Still there are cases in which the bronchitis comes into the foreground on account of excessive secretion or a cough. I remember a case, for instance, in an old lady living in a malarial region. She repeatedly manifested, with a tertian intermittent, so intense a bronchitis, that the physicians were always deceived and diagnosticated bronchitis, influenza, etc., until the further course, characterized by typical paroxysms and the prompt reaction to quinin, placed the diagnosis beyond doubt. The expectoration was exceedingly copious and mucopurulent. Over both lungs, but most marked over the lower lobes, medium-sized moist râles were audible. The percussion-note was normal. The pleuræ never seemed to participate—at least, pain and pleuritic friction râles were absent. The bronchitis persisted during the apyretic intervals, but was then slighter. It disappeared with the paroxysms or a few days later. It may be worth noting that this case manifested a marked inclination to diseases of the respiratory tract in general. In the course of two years the patient passed through two attacks of croupous pneumonia and frequently suffered from a mild bronchitis.

Similar observations have been made by other writers. Heinemann frequently saw in Vera Cruz coryza, catarrhal bronchitis, and marked dyspnea go hand in hand with acute malaria. After repeated attacks of this kind the bronchitis may become chronic, and, separated from its original cause, progress independently.

Triantaphyllides observed a number of cases with asthmatic symptoms in which the blood showed malarial parasites, though neither asthma crystals nor eosinophile cells could be found in the sputum.

Grasset has collected in his thesis several cases of this kind. In some, emphysema of the lungs occurred, which, in my opinion, should not be considered the result of the malarial bronchitis (Grasset to the contrary notwithstanding), but of a natural predisposition. At least it is difficult to imagine that a complete emphysema with barrel-shaped thorax could develop, as in one of his observations, on account of a bronchitis of two to two and one-half months' duration.

The question of the frequency of chronic bronchitis in cachectics has been discussed.

Although catarrhal affections of the bronchi are more numerous, pneumonia is of more interest on account of its greater pathologic dignity.

Pneumonia may complicate malaria in any of its stages, though it is most frequently associated with the cachexia, in which it constitutes one of the chief dangers.

In order to prevent misunderstanding, we wish expressly to insist that there is no proof that the malarial virus can produce a croupous infiltration of the lungs. In the section on Pernicious Fevers we described the pneumonic remittent and intermittent. In these we found only a swelling of the mucous membrane, associated with profuse secretion of mucus, serum, and even blood into the fine bronchioles, but no deposit of a fibrinous exudate.

The cases of intermittent pneumonia described in the old literature—*i. e.*, not with an intermittent fever, but with the disappearance of all objective and subjective symptoms during the apyretic interval, and a recurrence during a new paroxysm—are regarded by modern observers of the widest experience (Colin, Jaccoud, Roux, and others) as errors due to defective methods of examination. It is scarcely possible to conceive that a solid infiltration of a lobe would vanish in a few hours and return as quickly.

In Grisolle's "Traité pratique de la pneumonie" (1841) may be found the old literature on this subject. Injustice has been done to Grisolle by the assertion that he defended the occurrence of intermittent pneumonia. Grisolle states that he himself observed no such case. All he does, therefore, is give an intelligent résumé of the observations of others. He expressly affirms that the crepitant râles may cease during the apyrexia, to appear again during the paroxysm, but denies that the hepatization could retrogress within hours, to appear again suddenly with the corresponding physical signs.

From recent times we have no communications relative to this—at least, none that would stand criticism. Tartenson's view that the majority of croupous pneumonias are due to malarial infection is mentioned only as a literary curiosity of to-day.

Malarial pneumonia must not be confused with the uncommon croupous pneumonias that show, instead of a typical continued, an evident intermittent or remittent fever. These pneumonias have nothing to do with malaria, and I cannot agree with Tartenson when he asserts that "this form is observed in its full development only at the time of an epidemic of intermittent fever." I have several times seen these cases in individuals entirely free from malaria, and living in non-infected regions. Further details relative to these pneumonias may be found in the works of Gerhardt, Jaccoud, Bertrand, and Clark.

As previously stated, all types of malaria may be complicated with croupous pneumonia, yet these pneumonias are always mixed infections.

The complication of an acute malaria with pneumonia is no frequent occurrence, yet in regions in which malaria is endemic an epidemic of pneumonia may occur at the time of a malarial epidemic, and then both affections associate readily (Constant, Grifoulière).

The symptoms of this double infection are naturally made up of the symptoms of the two components. There are added, therefore, to the symptoms of the malarial affection, pain in the side, tormenting cough, rusty sputum, and other physical signs.

The course of the fever in these double infections deserves some attention. This is irregularly remittent, rarely intermittent. Ordinarily the two fevers are so interwoven that the curve fails to separate them. These are the cases for which Torti employed the expression, "proportionata," yet it sometimes happens that the curve shows a comparatively high level, with regular intermittent dentations. Marchiafava and Guarnieri and Antolisei observed pneumonias complicating acute malaria that ran their ordinary fever course.

The *subjective* symptoms are usually marked. They increase on the occurrence of an intercurrent malaria paroxysm, the three phases of which may be sometimes, but not always, recognized. The *objective* signs of pneumonia are not altered, whether or not a malarial paroxysm is in progress, and these continue until the pneumonia has passed.

The sputum is usually markedly hemorrhagic, and shows sometimes, besides the diplococcus of pneumonia, malarial parasites (as I have observed in one case). The parasites pass into the sputum with the red blood-corpuscles. According to Bignami, the parasites occur in the sputum but seldom, because the infected blood-corpuscles adhere to the walls of the lung capillaries, in the same way as in the cerebral vessels. That malarial parasites are found in the blood scarcely needs mention.

With timely diagnosis, the malarial infection may be broken up by quinin, while the pneumonia runs its ordinary course unhindered. The pneumonia appears either simultaneously with the malaria, when the first chill may mark the beginning of both diseases, or only after several malarial paroxysms have passed. In the latter case the pneumonia may set in with some of its characteristic symptoms absent, and develop under such slight subjective symptoms as to be readily overlooked, especially when the lungs are not examined daily.

The two greatest investigators of malarial pneumonia, Catteloup and Morehead, advise, therefore, that malarial patients be examined even as thoroughly and diligently as patients suffering from other severe diseases, otherwise the most serious mistakes are inevitable. In some cases it may be very difficult to decide whether the malaria or pneumonia began first.

The prognosis of this complication is naturally worse than that of pneumonia or of malaria taken separately—in fact, experience shows a rather considerable mortality. In special cases the age and constitution of the patient are of importance, as well as the extent of the infiltration and the kind of malarial infection. If the last is by parasites of the second group, and if other severe symptoms arise, the prognosis is naturally aggravated. The prognosis is especially unfavorable when the malaria is in itself pernicious; if, in other words, a comatose algid or choleraic pernicious fever is complicated with croupous pneumonia. In such cases a fatal termination is almost inevitable.

Our own case—double tertian with croupous pneumonia:

Ferd Säfer, aged forty-five, admitted to the hospital at Esseg August 4, 1892. He states that he has had daily for four days, about midday, a violent chill, followed by fever, but no sweating. Likewise, for the same length of time, a cough without expectoration. He complains, besides, of intense headache and pains in the limbs.

Status præsens at 4 P. M.: Medium-sized, pretty robust man; temperature, 40°; pulse full, 112; respirations, 40. Patient very restless, turning from side to side in bed. Pupils contracted. A mere touching on the bones, especially in the region of the knee-joint, is very painful. On percussing the tibiæ the patient draws himself together with the pain.

On the left, anteriorly from the clavicle down, dulness, with somewhat of a tympanitic note; otherwise percussion normal. Over the area of dulness loud bronchial inspiration and expiration, with moderately profuse, sonorous râles. Vocal fremitus is increased. Over the aorta a systolic and diastolic murmur. Splenic dulness extends to the border of the ribs. Palpation of the organ was unsuccessful on account of the superficial breathing.

In the blood, numerous tertian parasites in two generations. The first fully developed, large; the second, about twenty-four hours old, and filling only half the blood-corpuscle. Enormous numbers of flagellate organisms. Active pigment and ameboid movement. Many fragmented fever forms.

7 P. M.: 0.33 quinin mur.

August 5: During the night, a profuse sweat. Morning, 6 A. M., 0.33 quinin mur. Temperature, 8 A. M., 36.4°; pulse, 85; respirations, 30. Dulness similar to yesterday, the râles more numerous, subcrepitant. No expectoration.

In the blood, numerous large parasites, some vacuolated, with immotile pigment, a few dropsically enlarged, with actively swarming pigment. Numerous intraglobular parasites, one-half to three-fourths the size of a red blood-corpuscle, completely immotile, and with pigment likewise at rest. Further isolated torn forms.

One sporulation form with scattered pigment; four large spores and numerous small granules.

Midday, 1 P. M.: A very mild chill.

3 P. M.: Temperature, 37.2°. Patient expectorated for the first time on coughing. The expectoration consisted of large, yellow, consistent clumps, intensely hemorrhagic, sometimes bright red, again brownish red.

Microscopically in the sputum, besides diplococci, very many well-preserved blood-corpuscles, with between them, here and there, a shrunken parasite, and large cells filled with rough granules or yellowish flakes, together with pigment and dead parasites. In one of these a parasite was found with actively swarming pigment.

In the blood many deformed large parasites in the act of disintegration; likewise isolated sporulation forms. The pigment which they contained was at rest, or showed very little movement. Many broken-up quinin forms. Isolated parasites half developed, also motionless. Since quinin was administered, no flagellate organism was seen. Therapy each morning and evening, 0.33 quinin mur.

August 6: During the night, a profuse sweat.

3 A. M.: Violent headache, which disappeared toward morning. At present quite exhausted. Temperature, 36.4°; pulse 86; respirations, 28.

Still more dulness on the left side anteriorly in the second intercostal space. In the same place, undefined breathing, no râles. On the left posteriorly, alongside the scapula, a small area of dulness, with indefinite breathing. Sputum like yesterday.

4 P. M.: Temperature, 37.5°.

August 7: 8 A. M.: Temperature, 36°; physical signs in the lungs no longer perceptible. In the blood, apart from a few melaniferous leukocytes, nothing pathologic.

The patient left the hospital a few days later cured.

In cachectics pneumonia plays a much more striking and, we might say, legitimate rôle. As previously stated, cachectics suffer very frequently from chronic bronchitis, but show too an especial susceptibility to pneumonic infiltration.

It is a unanimous observation that cachectics suffer from pneumonia most frequently during the cold half of the year (Catteloup, Colin, Oldham, Roux, and others). In Algeria the majority of cases occur, according to Catteloup, during the months from November to March. Oldham saw numerous cases in Bahawulpur (East India), where differences of temperature of over 40° are not uncommon between day and night.

North winds in the malarial regions of the northern hemisphere carry with them the greatest danger to the cachectic.

The *symptoms of pneumonia* in cachectics have been studied most thoroughly by Catteloup. Later we had a magnificent treatise from Hadji Costa. The disease simulates in all details the pneumonia ordinarily seen in the old, the debilitated, drinkers, scorbutics, etc.

The initial chill and pain in the breast are frequently wanting; likewise the rusty sputum; though again the sputum is intensely hemorrhagic. The flushing on one cheek is sometimes the only suggestion of its appearance (Colin). Slight stupor is often present, and severe prostration or a typhoid condition may dominate the picture from the beginning. As Maclean and other writers affirm, both lungs are frequently affected. Besides the areas of infiltration, which are discovered by percussion and auscultation, we often find areas filled with serum, presenting symptoms of partial edema of the lungs. The fever is ordinarily moderate, and is of an irregular remittent type.

According to Kelsch and Kiener, there is frequently a very troublesome feeling of constriction in the hypochondria, due to congestion of the liver and spleen. Loss of appetite, a subicteric discoloration, vomiting, diarrhea, meteorism, hematuria, and hemoglobinuria are not uncommon accompaniments. In addition, we usually see nervous symptoms, like delirium, agitation, carphologia, and adynamia.

The course is frequently protracted, and may last ten to twelve days. The physical signs continue often one to two weeks after the fever.

The termination is fatal. Colin estimated for Rome, 60 per cent. mortality. Kelsch and Kiener had in their material about 78 per cent., and Hadji Costa lost 7 out of 14 cases.

The pneumonia of cachectics shows a great tendency to go over into gangrene or abscess. Complications like pleuritis, pericarditis, and meningitis are relatively frequent.

Not rarely it terminates in chronic interstitial inflammation, with shrinking of the parenchyma and the formation of bronchiectases. The prognosis, therefore, is to be regarded as *valde dubia.*

Bronchopneumonia is likewise frequent in cachectics, and chronic interstitial pneumonia, with shrinking of the parenchyma and dilatation of the bronchi, very frequent. Heschl first drew attention to this latter, and since then other French writers have taken up the subject (Charcot, Lancereaux, Laveran, Grasset, and others).

The contraction of the lungs develops either insidiously, and is then perhaps the result of bronchitis and peribronchitis, or it occurs as the outcome of a pneumonia.

Yet in a number of published cases, as the autopsy records show (see, for instance, Grasset), tuberculosis played an undoubted rôle.

A peculiar disease of the apices of the lungs has been described by de Brun, which he often observed in Beirut in youthful malarial cachectics. Its symptoms were dry, often tormenting cough, dulness, bronchial breathing, yet no friction sounds and no râles. The condition came and went with the paroxysms of fever, though in other cases it remained for a long time with slight fluctuations of severity. Occasionally there was added a diffuse bronchitis with sonorous râles limited to the apex. Tubercle bacilli were never found, though Laveran's organisms appeared in the blood.

In two cases on which postmortems were made no changes were found in the apices, and de Brun assumes that the disturbances were entirely the result of congestion (?).

Unfortunately, he has published no complete case history, so that it is difficult properly to judge of his assertions.

Pleurisy occurs apart from pneumonia only accidentally, and is rarely a complication of malaria.

Hertz reports a case of tertian with pleurisy in which the friction râles disappeared on the apyretic days, though it is scarcely conceivable that the fibrinous deposit could be so rapidly absorbed. According to Steudel, blackwater fever is frequently accompanied by pleuritis sicca.

Tuberculosis of the lungs occurs in malarial patients at least as frequently as in the non-malarial. The assertion made in former times that malaria and tuberculosis excluded each other (Boudin) doubtless depends on the fact that malarial regions, on account of their general climatic conditions, are more favorable to the respiratory organs. As a consequence, in these countries, tuberculosis plays a less dominating rôle. The smaller number of tuberculosis cases in Algeria in comparison with France is to be attributed, therefore, not to the malaria, but to the climate. The experience of the Roman pathologists is probably more correct, namely, that the debilitated malarial patients offer an especially favorable soil for tuberculosis. Others have arrived at the same conclusion.

Nor are all malarial countries spared tuberculosis. In India both diseases occur side by side; the same is true of Tongking, the Antilles, Guiana, etc. (see Jousset). Carsten actually asserts that phthisis is more frequent in the tropics than in temperate and cold climates.

DIGESTIVE TRACT.

The mucous membrane of the *mouth*, and especially of the gums, sometimes undergoes marked changes in chronic malaria. Loosening of the teeth, hemorrhage, and gangrene may occur. These complications are seen particularly in persons enfeebled by insufficient nourishment or overwork, though they sometimes belong to the epidemic of a definite year and accompany it as a complication.

Under the same conditions the *parotid gland* may be the seat of a suppurative inflammation. Lancisi reports a malarial epidemic, tertian in type, at the beginning of the eighteenth century (1709–1710), which manifested the following symptoms: after the third or fourth paroxysm, intense headache, followed by jactitation, coma, a hemorrhagic exanthem on the skin, severe epistaxis, and parotitis, the last often producing death by suffocation.

Since then parotitis has been repeatedly described as a serious complication in severe malarial epidemics.

We have discussed, in numerous places on the preceding pages, how frequently the functions of the stomach and intestines are disturbed in the course of acute and chronic malaria, and especially cachexia.

Here we will only add that when the original infection was prolonged, these functional disturbances often persist for a long time after it has passed.

These disturbances are of various kinds. On the part of the stomach, there is frequently a want of appetite, a feeling of weight after eating, pyrosis, and a distaste for certain foods, especially fat. These symptoms, according to their combination, indicate atony of the stomach, chronic gastric catarrh, or atrophy of the gastric mucous membrane.

The *intestinal disturbances* express themselves in an inclination to meteorism, constipation, or more rarely diarrhea. They may torment the patient for years after the malarial infection has terminated. In all cases we should endeavor to find out whether they are expressions of a local functional or anatomic disease of the gastro-intestinal tract, or are secondary symptoms from disease of the portal system. This last is not rare after malaria, or even during its course, and is, therefore, always to be kept in mind.

A rare occurrence is intermittent hemorrhage from the intestine or intestinal hemorrhage at all during the acute infection (see p. 300). Cases of this kind were observed, among others, by Frerichs and Bohn. They become of importance on account of the diagnosis (possible confusion with typhoid fever) or treatment. Quinin does wonders in these cases.

Acute ascites is even more rare. It develops either in cachectics, as the result of a pyelothrombosis, or in acute cases, possibly as the result of occlusion of the portal capillaries by melaniferous cells. De Brun assumes for these cases a congestion of the peritoneum.

After the thorough investigations of Bertrand and Fontan, it has been determined that the so-called Cochin China diarrhea has nothing to do with malaria.

Diseases of the Liver.—It is undoubted that in a number of cases malaria lays the foundation for progressive disease of the liver. I have repeatedly observed enlargement of the organ, with a painful feeling of tension, in acute and especially chronic infections. These symptoms are due to hyperemia of and a deposit of pigment in the organ. They disappear in the majority of cases and leave no trace after the pigment has been excreted.

According to Kelsch and Kiener, the *hepatomegaly* of cachectics, the result of the overloading with pigment, may remain for a long time, even persistently, on account of the functional activity of the organism being so depressed that elimination of the pigment does not take place, or at least not to any great extent. We frequently see, therefore, in cachectics a large liver, producing a feeling of weight and tension in the right hypochondrium.

Disturbances on the part of the gastro-intestinal canal are, as a rule, simultaneously present, as loss of appetite, nausea, feeling of weight in the stomach after eating, irregularities in bowel movements, etc.

Another frequent condition of the liver seen after long infections is *atrophy*. This has been described by Haspel, Frerichs, Kelsch and Kiener, and others. We shall see later that this atrophy in malaria is not always attributable to the same causes, and that the structure of the organ does not always show the same changes. It follows, therefore, that the symptoms of atrophy of the liver are not always the same, and that it is difficult to give a general description appropriate to all conditions.

The proof of atrophy by physical signs is always unsatisfactory, on account of the more or less marked ascites usually present. This is frequently so profuse and develops so quickly that puncture after puncture is necessary. If, after its evacuation, the diminished size of the liver is recognized, the question still remains whether this is the result of simple atrophy or of cirrhosis. Only under especially favorable conditions, and with very thin abdominal walls, is it possible to decide whether the surface of the liver is smooth or finely granulated. In the first case we would likely have to do with a simple atrophy.

In atrophy icterus is wanting, though it may precede the beginning of the condition. The stools are usually diarrheic, and manifest but little color. The urine, too, lacks bile coloring-matter.

The appetite is, as a rule, severely depressed; the food eaten is badly borne and sometimes vomited. Hematemesis and melena are occasionally observed. The general appearance is that of marked marasmus. In the minority of cases there may be slight symptoms of portal obstruction, though usually these are wanting.

The smallness of the liver, as evidenced by percussion, together with the general appearance and the absence of icterus, usually indicates the diagnosis of atrophy, or, at least, permits it to be conjectured.

Cirrhosis of the Liver.—The majority of observers agree that malaria may be the exciting cause of cirrhosis of the liver. There are differences of opinion only in regard to the frequency of the condition, and in regard to whether or not the cirrhosis thus provoked has particular characteristics.

The first observations on malarial cirrhosis come from Haspel, yet these are limited to a simple description of the macroscopic appearance of the liver at autopsy, without a further study of the nature of the condition.

We owe to Frerichs the statement of the fact that there are cases of Læennec's cirrhosis in which the anamnesis showed no misuse of alcohol, but, instead, a long-continuing intermittent, which probably played the same rôle. Yet Frerichs asserted that the granular liver was rare in individuals who succumbed to malarial cachexia. Bamberger adopted Frerichs' opinion on account of encountering similar cases. Colin frequently observed enlargement of the liver, with increase in the connective tissue and consequently with increased consistence, yet rarely granular cirrhosis. Lancereaux also gave his attention to this subject, though the most thorough investigation comes from Kelsch and Kiener. Among the Italians, Tommasi, Cantani, and Cardarelli put themselves on the side of malarial cirrhosis.

Still, opposition is not wanting. Marchiafava and Bignami have especially pronounced against the development of cirrhosis as a result of malaria. In their experience Læennec's was especially rare, the hypertrophic with icterus somewhat more frequent. Their principal argument, as will be mentioned again in the anatomic part, was based on the differences between the histologic structure of the liver tumor after malaria and that of cirrhosis.

It cannot be denied that the arguments on both sides, supported as they are by large experiences, deserve attention. Considering the many-sided etiology of cirrhoses and their protean histologic structure, overthrowing every outline made for them, much more work will be required before the question is decided.

In particular cases of cirrhosis it is not always easy to determine whether or not malaria played an etiologic rôle. The misuse of alcohol is so wide-spread that it usually comes into consideration. Only when it can be disposed of is the way clear. Unfortunately, the majority of cases in the literature suffered from this concurrence of alcohol. The cases in which it was entirely excluded are very few. Frerichs could point to only a single one.

As precarious as the matter is in the case of Lænnec's cirrhosis, it is even much more so in the other forms, especially the different subclasses of hypertrophic and biliary cirrhoses, since the etiology of this category of liver diseases is uncommonly rich in material. Gallstones, gastro-intestinal and general infectious diseases, metallic poisons, alcohol, autointoxications, diabetes, and malaria have all been brought forward as exciting causes. In tropical regions these are increased by dysentery and certain climatic-telluric influences not yet sufficiently understood.

Despite all this it seems permissible, from the evidence before us, to conclude that malaria may be the cause of Lænnec's as well as hypertrophic biliary or mixed cirrhosis.

Lancereaux, and also Kelsch and Kiener, go further and assert that the malarial cirrhosis manifests particular histologic characteristics which differentiate it from other cirrhoses. The last two express themselves as follows*: "Chaque fois que nons avons mis en parallèle la série de préparations de notre collection qui se rapporte aux hépatites d'Algérie avec celle qui se rapporte aux hépatites nostras, nous avons été frappés de leur dissemblance." To go into the details of this question would lead us too far. In the anatomic part we will recur to the subject.

I have sifted the cases of cirrhosis of the liver that came under observation in the first medical clinic in Vienna during the last fifteen years and find the following: Among 65 cases of atrophic cirrhosis without icterus, there were 6 in whose history malaria occurred. Of these 6, 5 were more or less strong drinkers. In the one case remaining the anamnesis showed (apart from a typhoid fever) a malaria lasting three years, which might be regarded as the cause of the cirrhosis, yet this case is not absolute, since it never came to autopsy.

Among 46 cases of cirrhosis with icterus five showed a long-lasting malaria. Of these, one must be excluded on account of potus and paroxysms of pain that were possibly gall-stone colic, leaving four cases, which corresponds to a percentage of 8.7 per cent.

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* *Loc. cit.*, p. 741.

The liver cirrhosis develops either immediately subsequently to the malaria or after a shorter or longer interval, sometimes amounting to years. It usually progresses gradually, with occasional improvement, until toward the end, when its advance is rapid.

I would like to call attention to a little matter that frequently struck me in practice. It applies to the genuine Hanot's cirrhosis, as well as to the other forms described as biliary. These cirrhoses not rarely begin with a frank intermittent fever, usually quotidian in type. It was introduced into the literature by French writers under the name "fièvre intermittente hépatique." This fever presents not the slightest difficulty in diagnosis if it begins when the other symptoms of the disease—icterus, tumor of the liver and spleen—are developed; yet there are cases in which this fever constitutes the beginning of the disease, and in these a confusion with malaria is not impossible, only, however, by ignoring the blood examination. If, following this, the symptoms of cirrhosis gradually appear, the second error may be made and this cirrhosis diagnosed as malarial cirrhosis.

The symptoms and course of malarial cirrhosis are naturally very different, depending on whether Lænnec's, Hanot's, or a mixed form is present.

We must deny ourselves the pleasure of going further into the symptomatology of this condition, and content ourselves with adding that Lancereaux has drawn a special picture for malarial cirrhosis which corresponds to Hanot's form. Though this may apply in a number of cases, a study of the literature shows that it cannot be considered the rule. Kelsch and Kiener, for instance, expressly insist that icterus rarely comes into the symptom-complex, and that ascites occurs in the majority of cases.

From these researches it appears that malarial cirrhosis, at least from a clinical point of view, possesses no special characteristics, but, on the contrary, presents as many differences in the symptom-complex as cirrhosis due to other causes.

Icterus, tumor of the spleen, hypertrophic and atrophic liver, ascites, gastro-intestinal and cholemic symptoms, hemorrhages from passive congestion or from an icteric hemorrhagic diathesis, dominate the picture in different combinations and in varying severity.

Whether the peculiar liver cirrhosis of children, endemic to India (Gibbons, Jogendro Nath Ghosk, Mackenzie), has anything to do with malaria, is very questionable. It is at present attributed, though not without opposition, to the bad nourishment of the children.

Amyloid degeneration of the liver will be discussed later.

Spleen.—The splenic tumor which develops in acute malaria decreases in size after the disease has passed, yet the organ scarcely ever becomes again normal in size, and we frequently meet people with enlarged spleens acquired years before from a mild malaria of short duration. This persistent splenic tumor is described as "ague cake." This enlargement, under ordinary circumstances, causes no disturbances. These set in only when the tumor is uncommonly large, or when it sinks down on account of its attachments becoming loose.

The size of the splenic tumor may be extraordinary. Cases in which it reaches to the umbilicus are seen daily. It can scarcely be called a rarity when it reaches to the pelvis and is supported on the pelvic bones. Under these circumstances the weight of the tumor—its pressure on the intestine, on the ureters, on nerve-trunks, etc.—causes various symptoms. The most frequent are: A feeling of dead weight in the left half of the abdomen on walking, standing, and riding, and pains in the left leg, sometimes associated with a coxitis position of this extremity.

When its attachments become loose, the organ may become movable to a varying degree and so cause various disturbances. As a rule, the organ sinks down only a little and then produces only slight disturbances or none at all. Still, cases have been described in which the spleen sank down into the small pelvis and produced symptoms of intestinal obstruction.

Severe symptoms of a violent character usually appear when the long-drawn-out pedicle of the spleen is twisted. The symptoms are those of an acute peritonitis or acute intestinal obstruction. The diagnosis is readily mistaken.

The wandering spleen is most frequently observed in the emaciated and run down; in women who have borne many children and have flabby abdominal walls, when it is usually in association with general enteroptosis.

Perisplenitis is a very frequent complication, and is the cause of the pain in the spleen complained of by many malarial patients, especially during the paroxysm. In some cases it occasions no disturbances, even when sufficiently marked to produce audible or palpable friction murmurs.

It sometimes develops only a long time after the malarial infection has passed. I observed a case in which the splenic tumor and the perisplenitis arose some time after a malaria and produced absolutely no disturbance. The patient succumbed to an intercurrent affection. The capsule of the spleen was thickened to a bony-like shell, over one centimeter thick, so that a saw was necessary to open the organ. The perisplenitis may lead to the excretion of a slight amount of fluid exudate into the peripheral cavity or even give rise to general acute peritonitis.

A condition, almost always fatal, though fortunately rare, is *rupture of the spleen.* It occurs almost exclusively in chronic splenic tumors, and is even then, in the majority of cases, the result of trauma. It has been observed several times in cases where patients in delirium threw themselves from a window and fell on the left side.

In one case of Haspel's the rupture occurred on vomiting, brought on by an emetic. Faunce saw a drunken man tumble on the street and so rupture an old ague cake.

The rupture is favored by different circumstances. Among the first of these we may mention a relaxation of the splenic tissue, such as accompanies acute infections (T. Colin), and relapses, especially in people with a chronic tumor. In the second place a marked inequality in the thickening of the capsule, on account of which the splenic substance is forced by the thicker to the thinner portions, which prove incapable of resisting the pressure. Finally, adhesions of the spleen to the diaphragm and ribs, on account of the non-yielding in case of a grave trauma from above or below.

The result of rupture of the spleen is hemorrhage into the peritoneum, the severity of which depends on the size and depth of the tear and other circumstances. If the capsule is not broken,—in other words, if only an internal rupture of the spleen occurs,—a subcapsular hematoma arises. E. Colin observed a case in which, on account of extensive adhesions, the blood failed to pour into the peritoneum, but instead made a track for itself through the diaphragm into the left pleural cavity.

The diagnosis of rupture of the spleen is associated with no great difficulty. The history of the preceding trauma, the tumor of the spleen, the sudden collapse with rapidly increasing pallor, the development of dulness in the dependent parts of the abdomen, the general tenderness on pressure over the abdomen, are sufficiently characteristic.

Death is usually rapid on account of the hemorrhage. In cases not immediately fatal a general peritonitis frequently develops. In some instances life has been preserved by a timely laparotomy.

Splenic abscess is a rare sequel. Fassina could find only seven cases in the literature up to 1889. To these he added two of his own. On account of this very small number, little can be said about its occurrence. Almost all cases were in cachectics. The symptoms were variable. In some cases localized violent pain, doughy edema, and redness of the skin, a fluctuating tumor, a pyemic fever refractory to quinin, suggested the diagnosis. In others pain was less pronounced and only symptoms of general emaciation, irregular fever, diarrhea, and voracious appetite were present. In one case of Mallet's the abscess ruptured externally. Lancereaux reported a case that showed metastases in the lungs and brain.

The course is principally dependent on whether a proper diagnosis has been made and timely surgical interference undertaken. In case there are good grounds for supposing an abscess, a trial puncture may be made in the hope of striking the chocolate-colored or red-wine-like pus.

Left to itself, the abscess is cured only when it ruptures externally or into the gastro-intestinal canal.

Zuber observed two and Doue one perisplenitic abscesses in old malarial patients. Hertz describes an abscess of the spleen that originated from an extravasation of blood. E. Colin calls attention to the fact that circumscribed hematomata of the spleen shut off by adhesions may be mistaken for abscesses.

Partial *gangrene of the spleen* has been observed by E. Colin in two cases. Necrotic shreds and even large sequestra of spleen tissue, without gangrene, have been frequently found in splenic abscesses.

Embolic infarcts are not uncommon, and during life occasionally cause severe symptoms (fever, chill, pain).

UROGENITAL SYSTEM.

Nephritis.—Nephritis constitutes one of the rarer sequelæ, though observations as to its frequency are considerably at variance.

These differences are due, in the first place, apparently to endemic causes; in the second place, to the fact that the clinical diagnosis of nephritis is made on different grounds by different people. Albuminuria is regarded as nephritis by some, when it may be only the result of stasis or parenchymatous degeneration (cloudy swelling).

Frerichs, for instance, saw on the coast of Friesland, numerous cases of malarial cachexia with ascites, yet none with nephritis, while Bartels observed in Kiel numerous cases of parenchymatous nephritis in malarial patients coming from Schleswig-Holstein and the shores of the North Sea. Kelsch and Kiener investigated the subject in Algeria and found all forms and grades of the affection.

Rosenstein bestows considerable attention on malaria and kidney disease. He estimates that of the cases of Bright's disease observed by him in Danzig, 23 per cent. were due to malaria. In northern Holland (Groningen), in spite of the great prevalence of malaria, he found this complication rare; in southern Holland, very frequent. He mentions, too, that Heidenhain observed a series of intermittent fever epidemics in Marienwerder, with neither dropsy nor kidney disease following, while in the last epidemic there was scarcely a case without secondary nephritis.

Soldatow, who had the opportunity of making 350 autopsies on malarial cases in Dobrudja, found nephritis very frequent. Wood and Atkinson likewise assert its common occurrence. In Bamberger's statistics of nephritis malaria plays a very secondary rôle. Among 623 cases of secondary nephritis only 13 could be attributed to malaria, yet he adds that this may be because malaria plays at most an unimportant rôle in Vienna.

Blackwater fever seems to be followed by nephritis no more frequently than the common forms. This is remarkable since, in addition to the noxious influence of the parasite, there is the irritation produced by the excretion of the dissolved hemoglobin. The form of nephritis produced by malaria varies.

Acute nephritis, according to Rosenstein, sometimes occurs during the course of quotidian fever, especially when the sweating stage is absent and is manifested by its usual symptoms (oliguria, blood, albumin, casts, edema, etc.), though the edema may be wanting. Rosenstein makes its duration two weeks to four months. He saw no case become chronic and no case end fatally.

Kelsch and Kiener likewise observed acute nephritis, and usually in the first period of malarial intoxication. It developed either during the course of the fever paroxysms or during convalescence, probably provoked by cold. According to them also the duration is from several weeks to several months. In the majority of cases the typical symptoms were present, together with the common sequelæ on the part of the circulatory apparatus. Fatal cases were observed repeatedly.

Subacute nephritis in the common form, represented by the "large white kidney," has been reported by Rosenstein as especially frequent in association with or following malaria. In regard to it he says*: "Particularly after intermittent, I have observed typical cases which, without further examination, would certainly be regarded as amyloid. Investigation of the anamneses showed that the preceding fever occurred usually in three different forms: In the first the paroxysms were incomplete in that, in case of a tertian type, there was a cold and a hot stage, but no sweating stage. In the second the paroxysms were complete, of tertian or quartan type, but few in number. After three or four such paroxysms an interval of several weeks occurred, during which the patients showed but slight general disturbances, in spite of the continuance of the fever in a latent form. They returned to their work until dropsy appeared simultaneously with albuminuria or preceding it. In the third, fever paroxysms of varying type occurred almost uninterruptedly for months (in one case even two years), and only with their cessation did dropsy and albuminuria come on. Dropsy is a constant symptom that I never saw wanting in nephritis produced by intermittent. The urine shows the characteristics belonging to the large white kidney, oliguria, high specific gravity, considerable albumin, and, among the formed elements, lymphocytes, fatty granular cells, and granular casts. I must mention as a peculiarity that the urine contains considerable urates, and, therefore, on account of its small volume, may appear, when cold, cloudy and loamy. The casts are frequently granular, due to impregnation with urates, and, on the addition of acetic acid, the rhombic crystals of uric acid become conspicuous."

Kelsch and Kiener likewise often observed the "large white kidney" following malaria (described by them as "néphrite à granulations forme aiguë").

Chronic nephritis in the form of secondary contracted kidney is not rarely seen in cachectics. It is regarded as a terminal form of the two previously named conditions. The uremic symptoms accompanying it may give rise to difficulties in diagnosis. The course of malarial nephritis is distinguished in no way from that of nephritides in general.

For the prognosis, we may refer to the observations just mentioned. Still we may add that Bohn rarely observed Bright's disease following malaria in children, yet when it did occur, it was always fatal.

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* *Loc. cit.*, p. 325.

Among the diseases of the external genitalia as the result of malaria we may mention *gangrene of the penis* and scrotum, and, in females, of the labia.

In the section on Cachexia we have already referred to this subject. We may add here that the gangrene usually runs its course entirely without pain. It may be limited to a relatively small area, and recover under scar-formation, or may spread rapidly to the mons veneris or the inner surface of the thigh, when the prognosis becomes serious.

Malarial orchitis has been described especially by French military physicians (Maurel, Girert, Calmette, Charvot, Bertholon, Schmit, and others). According to Martin, who saw a number of cases in Sumatra, we have to do in these cases with "a foudroyant inflammation of the male sexual organs (testicle and epididymis)." The testicle and epididymis are almost simultaneously affected by the inflammation under marked remittent fever. Cachectics and men who suffered previously from malaria are the victims. No trauma comes into play, nor does acute or chronic gonorrhea. The pain is more intense than in gonorrheal orchitis. Moreover, in the latter, the epididymis is usually primarily affected, and only later the testicle. The swelling may be marked, and not rarely reaches the size of a child's head. Under proper treatment it disappears more quickly than the gonorrheal orchitis, though it may lead to extensive suppuration of the testicle.

Martin states that he never saw thickening of the epididymis remain, though often hydrocele. The majority of other writers report a termination in atrophy of the testicle. Girert observed in Panama, among 350 malaria cases, 192 times orchitis with subsequent atrophy of one or both testicles.

Laveran is very skeptical in regard to malarial orchitis, and asserts that the majority of cases were probably ones of gonorrheal, parotitic, tuberculous, or, in the tropics, filarial orchitis.

We must add that an accurate blood examination for malarial parasites, as well as filaria, together with a careful weighing of other circumstances (gonorrhea, epidemic parotitis, tuberculosis, etc.), is demanded before a diagnosis of malarial orchitis can be made with certainty.

Fayrer frequently observed in India *hydrocele* as a result of malaria. (For disturbances of the bladder see section on Nervous System.)

Metrorrhagia is not rare during the paroxysms, and in case of pregnancy, may produce abortion.

Malarial Infection and Pregnancy.—Pregnancy constitutes no protection against malarial infection, notwithstanding older observations to the contrary. In a gravid woman the infection often takes on a severe form. The influences making for anemia in case of even light infection are more important in the pregnant woman than in others.

Abortion occurs very frequently. A. Weatherley reported at the Medical Congress in Calcutta that in India 46.6 per cent. of his cases aborted, while in England the frequency amounts to not more than about 3.56 per cent. Pellereau reports the same from Mauritius. The abortion does not require a fever paroxysm for its production. The fetus is usually dead before the abortion occurs.

Weatherley also finds sterility very common among the women in India, and he lays this at the door of malaria.

According to Chevers (India), the act of parturition often operates as an exciting cause in an outbreak of malaria, during which the lochiæ and milk secretion cease. Recovery occurs in the great majority of cases. The same was reported by Barker in New York. He had only one death among 47 cases (quoted after Roux). Blood examinations would be naturally very desirable in similar cases, since the possibility of septic infection is too great.

According to Emmett (quoted after Roux), subinvolution of the uterus and postpartum hemorrhage may occur.

HEART AND BLOOD-VESSELS.

The heart participates but little in the malaria process. Apart from light grades of hypertrophy and degeneration of the myocardium with dilatation encountered in cachectics, there is no lesion positively determined to be due to malaria.

French writers (Duroziez, Lancereaux) have endeavored to show a connection between endocarditis and malaria, but the number of their observations is so small that they cannot be regarded as convincing.

The systolic murmurs not infrequently audible at the different orifices during the acute infection, and likewise later, together with the increase in heart dulness, are symptoms common to all feverish conditions accompanied by anemia. They are "accessory" symptoms. Rauzier and Fabre have occupied themselves with this question.

According to Fayrer, rheumatism is a frequent complication in

India, occurring most commonly in the natives, but also in foreigners, though endocarditis is not associated with it.

He observed in Europeans resident for a long time in Bengal a condition which he describes as asthenia cordis. This consists in an uncomfortable sensation in the region of the heart, that at times may become so irritating as to wake the patient from sleep during the night. It sometimes recalls angina pectoris. The heart dulness is increased, the pulse arhythmic, the respiration dyspneic.

Aortitis, with subsequent neuritis of the cardiac plexus and angina pectoris, has been described as an effect of malaria by Lancereaux. The stenocardiac paroxysms are manifested by sharp pain in the chest, radiating to the arms, a flow of saliva, and diuresis. The inflammation is localized, at the beginning, to the aorta, and in contrast to ordinary arteriosclerosis, commences in the tunica externa, from where it passes over to the cardiac plexus, producing the paroxysms of pain.

When we consider that Lancereaux saw only two cases, both of which showed a narrowing of the coronary arteries, and in both of which the malaria preceded the aortic affection by many years, his conclusions give ground for skepticism, both in relation to the etiologic rôle of the malaria and the connection of the neuritis of the cardiac plexus with the stenocardia. Le Roy de Méricourt and Laveran both affirm that they have not observed a greater number of cases of angina pectoris in Algeria than in France; consequently they deny any connection between this affection and malaria.

Phlebitis; Venous Thromboses.—We have already mentioned, in the discussion of cachexia, that phlebitis of different veins with subsequent thrombosis has been frequently seen in cachectics with advanced anemia. It occurs usually in veins of the lower extremities; less often in those of the arms and the neck. Pyelothrombosis has likewise been observed, even though rarely; also cardiac thrombi.

NERVOUS SYSTEM.

The nervous system constitutes one of the principal points of attack. The typical intermittent paroxysm itself may in great part be regarded as the reaction of the vasomotor centers to the infection. In the sections on Pernicious and Latent Fevers cases have been mentioned in which nervous symptoms were added to the fever paroxysm, or were manifested alone, without, or almost without, the fever.

Here we intend to discuss chiefly those nervous symptoms which arise in the course of the attack or later, and continue a longer or shorter time after the acute infection.

No positive fundamental difference exists between the intermittent and persistent nervous affections. The same cause that produces in one case a fleeting syndrome may, on reinforcement or on encountering a special susceptibility, produce a long-lasting disturbance, and vice versâ. Consequently we have preferred to divide this subject among different sections than discuss it as a whole, while it corresponds better to the arrangement of our matter, though we will not deny that a section on the nervous disturbances alone would be, to a certain extent, more comprehensive and possess the advantage of less frequent repetition.

The nervous diseases following malaria have a variety of causes. In one case the cause may be a *cerebral hemorrhage*, due to rupture, during a paroxysm, of an arteriosclerotic vessel. Still, such an occurrence cannot always be regarded as a peculiar complication, since any physical effort or mental excitement might have provoked the hemorrhage quite as well as the malarial paroxysm. The occurrence of the hemorrhage, therefore, might really be accidental.

Yet a cerebral hemorrhage may actually be due to the malarial infection, as is evidenced by a case of Blanc's. This was an obstinately recurring quotidian in a young man. After repeated hemorrhages from the gums and nose, apoplexy with convulsions occurred, followed by death. In the brain a large subcortical and numerous capillary hemorrhages were found. The former had broken through the cortex and spread out under the meninges. No nephritis, no lues, etc. Yet a case like this is extremely rare.

In other cases it is not large, but very small, numerous capillary hemorrhages that cause the nervous symptoms. Again, they are the result of obstruction of the vessels of the brain or spinal cord by infected red blood-corpuscles or of processes in the ganglion-cells due to the action of the toxin. These conditions are all actual complications produced by the malaria.

From even this short enumeration of the causes we must realize the large series of widely different localized and diffuse processes that may take place in the central nervous system, as well as in its peripheral tracts. As a matter of fact, observation shows that the most different nervous diseases are produced, at least clinically, for the anatomicohistologic investigations are still too few to serve as a basis for conclusions.

This is undoubtedly the reason why neural pathologists have so far treated malaria in such an unsystematic fashion. Still, recently a change has taken place, and we may hope that in the not too distant future the nervous diseases following malaria will have the same careful consideration as those associated with other infectious diseases.

The very great majority of nervous complications occur in connection with estivo-autumnal infection, or, in other words, the parasites of the second group, though cases have been seen in connection with other forms—as, for instance, paralyses with quartan fever.

Though the nervous symptoms are ordinarily divided into intermittent and persistent, and we have not totally rejected this point of view, our division is based on the different parts of the nervous system. Still we may mention that a pure intermittence of nervous symptoms is much rarer than a persistence, even when, as is usually the case, they extend over only a few days.

The oldest observation on malarial paralysis is found in the splendid work of Joannes Fernel (1586). He regarded as their cause a pouring of bile into the spinal column and into the origins of the nerves.*

Focal Diseases of the Brain.—Among the malarial neuropathies, these are the most common. They consist usually in hemiplegias, either with or without aphasia; less frequently in paraplegias with aphasia, and rarely monoplegias. Sensibility may be either diminished or undisturbed; occasionally there is hyperesthesia. The paralysis may be one of relaxation or rigidity.

Suckling observed a very interesting case in which paraplegia and aphasia repeatedly came on several hours after the paroxysm. The anesthesia of the legs lasted only a few hours; the motor paralysis usually improved, so that the man could walk on the third day. Ouradou† observed, in the course of a comatose pernicious fever, an incomplete paraplegia with motor aphasia in which the disturbance of speech was still evident after several weeks; and a second case,‡ in which the paraplegia, with almost total motor aphasia, persisted four years after the pernicious attack.

Boinet and Salebert report a case of motor aphasia (without paralysis) which continued a month and then recovered completely.

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* Joannes Fernel, Universa Medicina, Lugduni, 1586, p. 259.

Causa paralysis.

Quinetiam alias cuius humor in spinæ medulla infixus paralysin committere potest: ac sæpe flava bilis hanc infligit, quum sub finem intermittentium febrium in spinam dorsi ac in nervorum origines effunditur.

† *Loc. cit.*, Obs. iv.

‡ Obs. vi.

Among the monoplegias we may mention Vincent's case with paralysis of the extensors of the fingers of the right hand and aphasia. The paralysis appeared under intense headache and fever several days after the patient had become apyretic. The symptoms disappeared in about seventeen hours. Boinet and Salebert mention a case of paralysis of the ulnar nerve with anesthesia.

In addition isolated cases of amaurosis, deafness, loss of taste and of smell, have been observed, though the first the most frequently (Sacchi). Motor irritative symptoms from focal disease are less common than the degenerative symptoms.

Tremor of the paralyzed extremities has probably been observed oftenest (Vespal). Choreic symptoms were observed by Maillot and Ouradou; tetany (?), by Wilckes.

Boinet and Salebert describe an interesting case of athetosis observed in a soldier in Tongking. After a series of malarial paroxysms a sensation of numbness in the right hand arose, followed by tormenting formication over both hands and all the fingers. Ten days after the last malarial paroxysm a new one with coma occurred. Two days later the right hand showed a typical athetosis. Sensation was diminished in the region of the ulnar nerve, but was little disturbed in that of the radial. The hand was powerless and could grasp no object. Sensibility of the forearm was fully preserved. The condition remained stationary.

Maillot describes* a case in which, after a comatose double tertian, contracture of the right arm occurred. The contracture forced the arm tightly against the breast. Verdan frequently observed in Wargla (Algeria) contracture of the extremities during the paroxysms.

Diseases of the Spinal Cord and its Continuations.—Affections of the spinal cord in the course of or after malarial infection, though not so frequent as those of the brain, are not especially uncommon.

Paraplegias of the lower extremities are comparatively the most frequent, and are often associated with disturbances of sensation, and sometimes, too, with paralysis of the bladder and the rectum. In some cases atrophy of the muscles has followed. Whether actual disease of the spinal cord, rather than a peripheral neuritis, played the rôle in these cases cannot be determined.

Csillag observed a series of pure paraplegias which developed during a severe subcontinued malaria, and persisted only a few days after the acute infection. Sensation was preserved. Ataxia was seen once; again, rectal paralysis. The patellar reflexes were diminished. Laveran, too, observed a case of paraplegia without disturbances of sensation and without bladder or rectal symptoms. Moreover, in this case the parasites were demonstrated in the blood, though we must add that the patient was also syphilitic. The paraplegia persisted in spite of quinin, mercury, and the iodids.

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* *Loc. cit.*, p. 95.

Much more rare are cases of successive paralysis in all four extremities. Maillot observed one case.* A tremor of the upper extremities was first noticed, followed by paralysis; later the same in the lower extremities. Sensation was gradually lost. Secessus involuntarii, paralysis of respiration, death. The autopsy showed the spinal pia and the cord, especially in the region of the cervical enlargement, markedly injected, and, at the level of the lower dorsal segment, a red softening, six to eight lines in diameter.

Two highly interesting cases of rapidly increasing paralysis with fatal termination were observed by Rangé in Benin.

The following is an abstract of one of these cases†:

L. M., aged twenty-one, twelve months resident in Benin, was admitted to the hospital at Porto Novo July 23 on account of blackwater fever. Previous to this he had had fever paroxysms every three months. He ascribes this last affection to exhausting work in the sun.

July 23: Temperature, morning, 39.6°; evening, 40.3°; bilious vomiting; pathognomonic urine; restless. Injection of quinin hydrobrom.

July 24: Temperature, 38° and 38.3°. Persistent vomiting. Considerable urine of a malaga color. General condition pretty satisfactory. Two injections of quinin.

July 25: Evident improvement. Temperature, 37° and 37.4°. Vomiting still continues. Urine clear, copious. Diarrheic stools. Two injections of quinin.

July 26: Temperature, 37.6° and 37.9°. Urine clear; vomiting less frequent.

July 27: Temperature, 38.4° and 37°. The vomiting, again more frequent, is exhausting the patient. Two quinin injections.

July 28: Temperature, 37.5° and 37.3°. Vomiting has ceased, but in its place singultus. Urine clear. One injection of quinin.

July 29: Temperature, 36.8° and 37.2°. The singultus has ceased, and the vomiting has set in again, yet the general condition is improved. The patient has an appetite. Quinin sulph. in pills.

July 30: Temperature, 38.8° and 37°; general condition improved.

Up to August 3 there was no change. At the afternoon visit he complained that he could not feel his legs. These were insensible to every irritation. The upper part of the thigh and the rump had retained slight sensibility. The patient was massaged, and a warm bottle was put to the feet. The temperature was normal; pulse quiet and rhythmic.

When we saw the patient again at 4.30 P. M. the anesthesia had progressed, and, further, the patient could not now move his legs. Both sphincters opened involuntarily. The paralysis rapidly advanced in spite of every effort, affecting the buttocks, the upper extremities, the neck, and finally interfering with respiration. The intercostal muscles and the diaphragm struggled against the paralysis, but in vain. The patient died at 5.30 P. M.

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* Obs. l, p. 252, *loc. cit.*

† Loc. cit., p. 268.

The second case progressed in an analogous way, as likewise a third case, observed by Dr. Mesnard.

Isolated cases of paralysis of the bladder with retention of urine during the acute infection are not rare. This may occur without pyrexia—in other words, latently (Marion).

The diagnosis of spinal disease as the result of malaria is often difficult in regions where beri-beri is simultaneously endemic. Especially cases with paraplegia may lead to error. If the girdle pain frequent to beri-beri, and never, so far, described in malarial paraplegia, is absent, or if the paraplegia quickly recovers under quinin, the diagnosis of malarial paraplegia is easy. Yet if pain and atrophy exist, it may be very difficult to make a diagnosis. It is impossible here to go into further details.

We have already described (p. 291) a case of Marchiafava and Bignami's with *bulbar symptoms.* These writers mention also in the same publication that they have several times seen similar bulbar cases, and that they always continue a longer time than the cerebral. Orlandi observed in five cases transitory bulbar symptoms following the paroxysms.

Diffuse Affections of the Central Nervous System.—Among these the chief place is occupied by a disease that imitates the complete syndrome of multiple sclerosis. On account of the rapidity with which this symptom-complex comes and goes it is impossible to conceive that its pathologic anatomy is the same as that of genuine "sclerôse en plaques." Yet the symptoms are so similar that it is scarcely possible to identify it with Westphal's "pseudosclerosis."

The malarial *multiple sclerosis* is relatively frequent. There are, even now, a sufficient number of observations, a part of which are based on a positive blood examination, to give this disease a legitimate place in nervous pathology. Among the observers we may mention Boinet and Salebert, Bignami and Bastianelli, Torti and Angelini, and Triantaphyllides. Torti and Angelini observed two cases. Both were in young adults, twenty-one and twenty-two years of age respectively. In one the first symptom appeared after an irregular malaria lasting three months. The patient was then apyretic, though the blood contained numerous parasites. The sclerosis syndrome developed rapidly—nystagmus, scanning speech, volitional tremor, exaggerated reflexes, etc. On administration of quinin most of the symptoms, together with the parasites, disappeared. Shortly after a relapse occurred, accompanied by the nervous condition. The symptoms, with the exception of the exaggerated reflexes, vanished again on renewed therapy. In the second case the sclerosis syndrome came on after a malaria lasting three months. Malarial parasites were found in the blood. Treatment for three weeks with quinin and arsenic resulted in recovery. Triantaphyllides published four cases; of which three promptly recovered, and the fourth persisted on account of treatment being begun too late.

Canellis reports the case of a man in whom multiple sclerosis developed after repeated attacks of malaria which proved refractory to therapy. According to Torti and Angelini, malarial sclerosis occurs under the following forms: (1) Those in which the syndrome comes and goes with the paroxysm; (2) those occurring after the attack and of variable duration; (3) apparently latent forms without fever.

If the previously quoted uncured case is to be ascribed to malaria, to these three categories must be added a fourth, namely, genuine chronic multiple sclerosis.

Isolated cases of *pseudotabes* have likewise been seen. The first case of this kind was described by Kahler and Pick as acute ataxia following malaria. After several sharp, typically intermittent quotidian paroxysms there occurred once, in place of the fever paroxysm, a dysarthria accompanied by marked ataxia of all four extremities. The patellar reflexes were abolished; the eyes showed nystagmus-like disturbances of coördination. The pupils were contracted, but reacted to light. The condition lasted only a short time and was followed by complete recovery. Even the patellar reflexes returned. Délwéze frequently observed in Jamaica cases of ataxia with visual disturbances which he regarded as malarial. The symptoms came and went intermittently, were equally frequent in men and women, and yielded to specific therapy.

Besides the syndrome of multiple sclerosis, that of *paralysis agitans*, *tetanus*, and *tetany* have been seen after malaria (Boinet). The observations are not yet numerous enough to form a judgment on these cases.

Raynaud's Disease.—Local asphyxia with symmetric gangrene. Raynaud's own cases showed malaria in their anamneses, though the discoverer did not assume any connection between the two diseases. After Rey and Marroin had published similar observations, Moursou stated that, from his personal experience, he believed that Raynaud's disease could be caused by malaria. Several cases reported since then seem to favor this view.

An especially suggestive and closely investigated case was described by Blanc. This was in a young boy suffering from severe chronic malaria. Algid symptoms appeared, and, during the paroxysms, the cooling and cyanosis of the surface of the body became striking. He later complained of pains in the bones, with formication over the cold, cyanotic toes. In the apyretic intervals the symptoms ameliorated, to become worse with every new paroxysm. Eventually gangrene of the toes set in. In the mean time the patient passed through two attacks of pneumonia. Local asphyxia does not necessarily advance to gangrene. The literature contains quite a number of cases in which it did not occur.

Ischemia of the tongue is described by Bérenguier as frequent.

Anomalies of secretion, like excessive secretion of tears, a discharge from the nose, ptyalism, a flow of milk, and a discharge from the urethra have been reported, both accompanying the paroxysms and occurring separately as latent symptoms (Schönlein).

Diseases of the Peripheral Nerves.—Syndromes probably dependent on a peripheral neuritis are not rare sequelæ.

Boinet and Salebert describe cases of evident peripheral origin, though the observers themselves regarded them as medullary. Among these are two of paraplegia with atrophy, lancinating pains, pain in the muscles, anesthesia, and diminution of the tendon-reflexes. Another of marked atrophy of the muscles of the buttocks and thigh that developed under violent pain at the close of a long malaria.

Cases belonging to this category were also seen by Combemale, Brault, Catrin, and others. A very beautiful case of polyneuritis of all the extremities in a man with chronic malaria was observed by Metin. Becker described a case of bilateral sciatic neuritis after malaria.

Daville frequently saw, in the New Hebrides, both during the paroxysm and before it, neuritis associated with sharp pains on the dorsum of the foot, about the malleoli, in the hips, in the joints of the hand, and in the elbows. Whether or not these disturbances are identical with the "rheumatic affections" reported by Fayrer from India must be left undecided.

Still less can we express any view in relation to the peculiar affection observed by Grierson, Malcolmson, MacKenna, Waring, Chevers, Playfair, and others in East India, in Burma, in Tenasserim, Penang, and Singapore, which bears the name, "burning of the feet." Grierson and Waring consider it malarial. The chief symptom consists in excruciating pain, occurring in paroxysms in the soles of the feet and often the palms of the hands. The patients sit on the bed, support their feet on cushions, and endeavor, by turning them inward, to avoid the slightest contact of the soles. The affected parts may be entirely dry, or may show a profuse perspiration. Sometimes, too, the legs are painful, especially over the tibiæ.

Heidenhain's peculiar case possibly belongs to this category. This was a woman with duplex quartan who manifested, during every paroxysm, an intensely tormenting itching and burning on the inner surface of both hands, without the slightest perceptible local lesion. The paresthesia ceased every time with the paroxysm.

Neuralgias have been frequently observed during and after malarial fevers in every nerve region, though most commonly in that of the trigeminus. They occur after similar pains have been manifested during the acute paroxysm, as well as when these are wanting. Griesinger observed, among 414 cases of intermittent fever, 13 times trigeminus neuralgia, 7 times general neuralgic pains in the head, once pharyngeal and once intercostal neuralgia. Verdan reported intercostal neuralgias as very frequent.

FUNCTIONAL NEUROSES.

Hysteria plays a certain rôle, inasmuch as when manifested during or after a paroxysm of intermittent fever, it may give rise to difficulties in diagnosis.

Neurasthenic disturbances have been observed in persons run down by frequent attacks (Triantaphyllides, *loc. cit.*). Sleeplessness is frequent both during and after the infection.

The rare *febris vertiginosa* may also be mentioned. This is characterized by a very severe vertigo at the time of the paroxysm. Triantaphyllides describes a special syndrome, occurring usually in old malarial patients, in which vertigo is the principal symptom. The vertigo is frequently very severe, and sometimes brings the patient to the ground. Periumbilical pains, dyspnea, palpitation, subsultus tendinum, vasomotor disturbances, pseudo-asthma, and angina pectoris occur as associated symptoms in the syndrome. In all cases a hysterogenic spot has been found near the umbilicus.

Psychoses have been repeatedly observed, both accompanying the attack and as sequelæ (Sydenham, Frerichs, Griesinger, Lemoine and Chaumier, von Krafft-Ebing, Pasmanik, Manson, and others).

Von Krafft-Ebing saw a remarkable case which manifested typical paroxysms of intermittent fever until, after a blow on the head, when an intermittent psychosis under the syndrome of epileptic confusion set in. Quinin and arsenic brought about recovery.

Manson's case is likewise very instructive. This was a man who came from Bombay to London and was placed in an insane-asylum on account of symptoms of insanity. The blood examination showed the presence of malaria, and specific treatment was followed by cure.

Ségard reports several cases of psychic disturbances. In one, acute mania with erotic outbreaks lasting three days after a malarial coma of fifty-two hours' duration. In another, a patient in the hospital already on the road to recovery, though still manifesting fever, was struck with a fixed idea that he was needed at the fort. Otherwise the man behaved very reasonably. In spite of strict watch he succeeded in getting to the window and throwing himself into the sea. A third, in which a patient (who previously had several ordinary paroxysms), one evening during a paroxysm was seized with hallucinations, rushed out and wandered around in the thicket the whole night. Next morning he returned to the station in an extremely exhausted condition. The same evening a similar though milder paroxysm with hallucinations occurred.

Pasmanik seems to have had the widest experience with malarial psychoses. Among 5412 malarial cases he found mental disturbances 106 times.

A hereditary influence was present in none of these cases, and alcoholism in only 4.8 per cent. All were conditions of depression. Their duration varied between four days and three months, except one of persistent dementia. Pasmanik found comatose-soporose conditions to be the most common in children. On exacerbations of chronic malaria melancholia arose, and in cachectics, simple melancholic and stuporous conditions. The worst prognosis was given by the delirium of cachectics, the result of a relapse.

ORGANS OF SPECIAL SENSE.

EYES.

Swelling and redness of the conjunctivæ and eyelids, associated with photophobia and hypersecretion of tears, are not rare in connection with latent supra-orbital neuralgias.

In addition, some writers claim that there is a specific conjunctivitis palustris, which comes and goes with the fever paroxysm, and which may occur alone as a latent form. There is in these cases only a hyperemia, not an inflammation, and the symptoms consist in redness, photophobia, hypersecretion of tears, with sometimes edema of the conjunctivæ and lids. Pain is wanting. The affection is usually unilateral (Puccinotti, Griesinger, M. Raynaud, de Schweinitz, L. Raynaud, and others). Baylot observed several such cases during an epidemic in Biskra; Verdan, in Algiers. Malarial scleritis and periscleritis palustris are mentioned by de Schweinitz.

The cornea sometimes participates in the infection through the herpes which accompanies the fever, in that vesicles occur simultaneously on the nose and the eyelids (Godo).

Different forms of keratitis have likewise been associated with malaria, as, for instance, the interstitial keratitis of cachectics, by Levrier, Sedan, a dendritic keratitis, possibly arising from herpes cornea, by Kipp. The latter observed in America 120 cases of this kind. In 90 per cent. of the cases the keratitis came on several days after the paroxysm. At the beginning small prominences appeared on the cornea, which broke down and gave rise to ulcers. These were serpiginous in form, with small prolongations. Hypersecretion of tears, photophobia, and pain were also present.

Similar observations have been made by Arlt, Poncet, Sedan, and others. In Millingen's cases (Constantinople) the ulcer, as well as its surroundings, was anesthetic.

Necrosis of the cornea in neglected cachectics has been reported by Fayrer.

Iritis was observed by Brown, especially in cases that suffered during the acute infection from hemicrania and attacks of vertigo.

Even iritis with hypopyon has been ascribed to malaria (Staub, Quaglino). Tangemann described one case of iritis associated with intense pain, conjunctivitis, and photophobia, which did not react to atropin and was cured by quinin.

Pupils.—They are usually, though not always, dilated during the paroxysms. Inequality of the pupils has been observed.

Visual disturbances produced by lesions of the fundus are, on account of their frequency and their more evident connection with malaria, more important and interesting.

Poncet assures us from his wide experience that every visual disturbance in connection with malaria is dependent on a retinochoroiditis (which may be perceptible only with the microscope) or on a hemorrhage in the ciliary region, even when the ophthalmoscope shows no abnormalities of the fundus. Nevertheless, for practical reasons, we will preserve the division of visual disturbances into those "*sine materia*" and those with evident changes. Still, we must add that the designation "*sine materia*" is to be taken *cum grano salis*, and applies only to the negative ophthalmoscopic finding *in vivo*.

Visual Derangements Sine Materia.—In this category we have a series of functional disturbances of the eye which are usually of short duration and pass with the paroxysm, but which may progress even to amaurosis.

Many such cases have been described, though, we must add, the great majority of them without the ophthalmoscopic findings. According to L. Raynaud, in whose thesis the entire literature of visual disturbances in malaria has been reviewed, and whom we intend in part to follow, Moraud (1729) was the first to draw attention to this subject. Storch (1838) speaks of an amaurotic latent. Since then numerous observations have been made by Testelin, Leber, Landesberg, Sulzer, de Schweinitz, and others.

Hemianopsia.—This may be unilateral or bilateral. Peunoff observed lateral hemianopsia preceding the paroxysms. De Schweinitz reported a case of temporal hemianopsia with malarial parasites in the blood which was cured by quinin.

Dyschromatopsia has been less frequently observed (Peunoff, de Schweinitz, L. Raynaud).

Hemeralopia, amblyopia, and amaurosis are the most common disturbances. Ségard met them frequently in Madagascar; Sulzer and Poncet mention them; and L. Raynaud gives several examples.

According to Sulzer's observations, the acuity of vision often manifests marked fluctuations in acute malaria, as well as in cachexia. The visual field is intact or slightly contracted concentrically. Central scotoma is rare. The visual disturbance is usually limited to the periphery of the retina, though the central parts are sometimes undersensitive. Contraction for colors is rare.

Visible Lesions of the Fundus.—*Ischemia* followed by intermittent amblyopia was first described by M. Raynaud; again, by Moursou (both times in connection with local asphyxia of the extremities). Ramorino and Decreu observed cases of ischemic intermittent amaurosis which were cured by quinin. The ischemia is characterized ophthalmoscopically by contraction of the vessels and pallor of the disk.

Hyperemia of the retina and of the disk was observed by Sulzer in 20 per cent. of the acute cases. Peunoff reported the same. We might say, in general, that hyperemia of the eye-ground is a common occurrence during the acute attack.

Hemorrhages on the retina are not rare in pernicious cases. They are located, according to Poncet, usually in the ciliary, though sometimes in the macular, region, or even in the macula itself, and then commonly along the large vessels. Even hemorrhages into the disk are not very rare. Lopez y Veitia found the hemorrhages usually arranged radially to the papilla, along the vessels, and observed them increase during the paroxysms. After resorption they leave behind pale spots (MacKenzie) or disappear and leave no trace (Sulzer). Guarnieri found hemorrhages twice on microscopic examination of the eyeballs from ten persons who died of pernicious malaria.

Optic neuritis and neuroretinitis have been frequently reported. MacNamara and Jacobi were the first to direct attention to them. Among the later observers we may mention Sulzer and Poncet.

Sulzer, who made his observations in Java, saw optic neuritis, especially in cachectics. As a characteristic subjective symptom, he described the already mentioned fluctuation in acuity of vision. This may rise from V $\frac{1}{10}$ within a few weeks to $\frac{1}{2}$–$\frac{2}{3}$, to return after a few days to the previous condition. The affection usually begins in one eye, but later goes over into the other. The field of vision is sometimes concentrically contracted. Hemeralopia and photophobia may occur. The papilla is swollen and dark red-grayish; the veins are tortuous; the arteries contracted.

Atrophy of the optic nerve following malaria was first observed by Kohn, and later by Galezowski, Levrier, Bull, MacNamara, Sulzer, and others. Sulzer found that 80 per cent. of his cases of optic neuritis terminated in partial atrophy. The symptoms are diminution of the central acuity of vision, with scotoma and dyschromatopsia.

Choroiditis.—Poncet declares that the majority of affections of the fundus in malaria are to be considered as retinochoroiditis. Levrier and Peunoff observed choroiditis with clouding of the vitreous.

Vitreous Humor.—Hemorrhage into the vitreous the result of a single paroxysm was reported by Kries. Bull observed 17 cases of similar hemorrhages, the majority unilateral. Almost all the patients were over forty years old.

Seely described a serous *infiltration of the vitreous* in chronic malaria. Sulzer found this condition several times. In one case blindness was produced in a night in each eye at intervals of eight days. Eventually the patient became able to count fingers with one eye when they were held very close.

Paralyses of the ocular muscles have been rarely observed, and then only in connection with other nervous symptoms.

Disturbances of accommodation have been described in the form of paralysis by Bull, in the form of a spasm by Stellwag and Stilling.

Hypersecretion of tears has been frequently observed in latent supra-orbital neuralgia, yet isolated cases have likewise been described in which it was present apart from the neuralgia, both during and before paroxysms.

Moursou saw a marine with paroxysms consisting of fever, vasomotor disturbances on the right half of the face, transient amblyopia, and hypersecretion of tears. Later this last symptom occurred alone without fever until cured by quinin. In regard to quinin amaurosis and the anatomic findings in cases of visual derangement, see the proper sections.

AFFECTIONS OF THE EARS.

These have been described by several writers among the complications of malaria. We have a record of such complications from Weber. Liel mentions an *intermittent otitis* as a form of malaria. It begins with sharp pain in the ear, coming on at night, a chill, sensations of fullness and ringing in the ears, and vertigo. These symptoms are followed by sweating, and by morning the condition has passed. The subsequent evening, or the second one after, there is a repetition of these symptoms, only in greater intensity. An exudation may now be found in the tympanic cavity. The tragus is insensitive to pressure. Puncture of the tympanum or spontaneous rupture does not relieve, but quinin cures.

Voltolini reported cases of an *intermittent neuralgia* of the ear cured by quinin: intermittent otalgia. We have only to add that in none of these cases was absolute proof brought forward to show that they were due to malarial infection. The intermittence of the paroxysms, the effect of quinin, and the now and then described tumors of the spleen, are by no means sufficient, as we have previously insisted. Only a positive blood examination, by excluding every accidental complication, can be regarded as convincing.

SMELL AND TASTE.

Transitory loss of both of these senses during malarial attacks has been occasionally observed.

DISEASES OF THE SKIN.

The symptoms on the part of the skin that ordinarily accompany the paroxysms, like herpes and urticaria, have been previously described. We may mention, as a rarer occurrence, a rubeola-like eruption, without conjunctivitis or subsequent scaling of the skin, observed by Segard. He also reports cases of intense urticaria with marked, erysipelas-like swelling of the face, hands, and feet. Doering mentions a case followed by urticaria and a pemphigus-like condition. Numerous cases of petechiæ, simulating the picture of morbus maculosus Werlhofii, have been observed epidemically. Steudel reported furunculosis as frequent after blackwater fever.

More or less marked *pigmentation* of the skin is often observed in malaria. Moscato described a case in a four-year-old boy with chronic malaria. The pigmentation was chocolate-colored and occurred on the lower extremities, the seat, the scrotum, the penis, and the forearm. The pigment was even found in the vessel-walls and in the rete mucosum. He designated the condition as partial postmalarial melanoderma.

Gangrene.—In discussing malarial cachexia, as well as the complications on the part of the digestive, respiratory, and urogenital tract, we repeatedly mentioned that gangrene not rarely developed in the course of these conditions. The literature on this subject has been critically sifted by Petit and Verneuil. They divide gangrene into associated and idiopathic.

The associated gangrene appears in connection with wounds and operations on malarial patients. Comeano, for instance, observed that shot wounds in malarial patients showed a tendency to become gangrenous. Fontan saw gangrene in a case of osteotomy of the ulna. Yet the cases in which wounds healed without complication are in the very great majority (MacNamara, Roth, and others), and the former cases may readily be looked upon as coincidences.

Idiopathic gangrene, however, manifests in a considerable number of published cases unmistakable relations to malaria (see also Raynaud's disease). Apart from the gangrene of the internal organs, it usually affects the most distal parts, like the nose, ears, fingers, and toes. The gangrene is usually dry. It is observed in the course of acute affections and in cachectics, with or without fever.

A severe case of dry gangrene of the nose, cheeks, and ears, after a malarial infection lasting four weeks, has been described by Fischer, and a similar one by Blaise and Sarda. According to Schtchastny, such cases are not infrequent in the Caucasus.

Moty observed in a cachectic a moist gangrene that spread over the whole of the left rump and eventually produced death; again, an interesting case of disseminated gangrene of the skin in an old cachectic. Echeverria saw disseminated gangrene in the course of continued malaria.

Laveran and Rogée each saw a case of dry gangrene as a sequel of endarteritis obliterans, in persons who showed malaria in their history. Whether there was a connection between the two affections cannot at present be said.

MUSCLES, BONES, JOINTS, AND LYMPH-GLANDS.

Diseases of the muscles in the course of malaria appear to occur only exceptionally; at least, but little is said about them in the literature. Steudel mentions an infiltration of the muscles after blackwater fever. Yet the muscles may undergo serious changes, as is shown by the microscopic investigations of Vallin. He found, among 10 cases that died of pernicious forms of malaria, 3 times granular, 4 times waxy, degeneration of the skeletal muscles. In 2 of the latter the appearance was exactly that seen in typhoid fever or smallpox. In the other 3 cases the muscles were normal.

Severe *myalgias* (muscular rheumatism) are frequently associated with acute malaria. They are usually located in the legs, the back, and the lumbar region. Verdan observed them in Wargla (Algeria) in at least one-third of the cases. For the sake of thoroughness, we call attention again to the muscular atrophies as a result of malarial neuritis.

Still less is written of the joints than of the muscles. Fayrer states that in the natives of India rheumatism seems to be a frequent complication, though, unlike ordinary rheumatism, this does not produce endocarditis. Verneuil may be correct in his conjecture that "malarial rheumatism" is rather neuralgia of the joints.

According to Heinemann, pernicious cases with excruciating pains and hemorrhages into the joints are not infrequent in Vera Cruz. The bones are frequently painful and tender in acute malaria. This may be so marked that the lightest percussion of the tibia is unbearable, and it frequently happens that malarial patients complain of nothing but this tormenting symptom. Pain in the last cervical and first dorsal vertebræ is not uncommon.

Lymph-glands.—Isolated cases have been observed, associated with swelling of different lymph-glands. Bodnar described 3 such cases. In one of them the malarial bubo even suppurated. Ségard's observations in Madagascar are of a more recent date. He observed several cases of malarial lymphadenia. This was characterized by fever and swelling of all the superficial glands, some of which suppurated. Since quinin caused a retrogression of the swelling, Ségard saw in them a localization of malaria. Unfortunately, blood examinations are wanting to give assurance.

BLOOD.

In malaria it is the red blood-corpuscles that first suffer. There is, therefore, no malaria without a decrease in erythrocytes and in the amount of the hemoglobin. To what degree this anemia may advance has been repeatedly discussed in the preceding pages; consequently we will not recur to the subject.

Progressive pernicious anemia has been repeatedly observed following malaria, and there is possibly a causal connection between the two. Fayrer and Ewart saw this sequela frequently, especially in gravid and nursing women and in children. These cases showed an especial tendency to hemorrhage and venous thrombosis. Thrombus formation in the right heart, usually with a fatal termination, was observed several times.

Whether other blood diseases, like leukemia, may be regarded as sequelæ of malaria, is more than doubtful, even though a number of cases show malaria in their history. On account of the wide distribution of malaria its occurrence is probably only a coincidence, and we will omit further details.

We have already mentioned that in the course of an acute and chronic malaria, and even cachexia, hemorrhages may occur from and into the various organs. Moreover, very trustworthy writers affirm that a hemorrhagic diathesis may develop as a sequel (Malherbe, Manson). This is characterized by hemorrhages from the nose, gums, stomach, and intestine, into the skin, etc., all of which may be intermittent; or actual hemophilia may arise.

Postmalarial Hemoglobinuria.—In considering hemoglobinuria in this section, we assume that the important factor in the disease is a solution of the erythrocytes; in other words, that we have to do with a disease of the red blood-corpuscles. The excretion of the dissolved hemoglobin by the kidneys is, therefore, only a symptom of the real condition; the hemoglobinemia, in the same way as jaundice, is only a symptom of obstruction of the biliary passages. Still we must not forget that some writers (Pellarin and others) locate the seat of the disease not in the blood, but in the kidneys, in that they regard renal hemorrhages (apoplexie rénale) as the source of the hemoglobinuria, though we have not the slightest doubt that systematic examination will demonstrate that in the great majority of cases the solution of the erythrocytes takes place in the circulating blood.

Postmalarial hemoglobinuria may be divided into two groups, namely:

(*a*) Essential postmalarial hemoglobinuria.

(*b*) Postmalarial hemoglobinuria the result of quinin.

Essential Postmalarial Hemoglobinuria.—In regard to essential postmalarial hemoglobinuria there are but few convincing observations. Murri's case is probably of most value, because accurately controlled. This was a girl who suffered a long time from malaria and who was successfully treated with quinin. One day, after the administration of quinin, a paroxysm of hemoglobinuria occurred. After this she repeatedly manifested fever with hemoglobinuria, without the slightest trace of parasites on the most careful examination and without taking quinin or any other medicament in advance. After a short time the paroxysms ceased.

In this short description the characteristics of the condition stand out clearly. We have to do here with a hemoglobinuria in a person who suffered previously from malaria that manifested itself under more or less severe general symptoms, apart from the action of medicaments, cold, etc. Much more frequent, in fact, the cause of a great part of the cases of blackwater fever is—

Quinin Hemoglobinuria.—In the discussion of blackwater fever Tomaselli's observation was mentioned. According to this there are persons previously or at the time infected with malaria who manifest a paroxysm of fever with hemoglobinuria after every administration of quinin, no matter how insignificant the amount. In a small number of cases the quinin produces the paroxysm even when the malaria has existed only a short time, and occasionally one dose is sufficient. Yet the great majority of cases last months and years, during which the quinin is taken without bad results before a paroxysm is produced. On account of the rarity of the condition, in contrast to the extraordinary frequency of malaria, Tomaselli insists that an individual predisposition must be assumed. This conjecture is strengthened by the fact that several persons closely related to one another have been repeatedly found suffering from the same affection. This individual predisposition may be, therefore, congenital, possibly even hereditary. Vincenzi saw a case in which quinin, administered for the first time in early childhood on account of malaria, produced a paroxysm of hemoglobinuria and in which the idiosyncrasy against it remained unchanged. In cases like the last the malaria perhaps plays a more subordinate rôle, the principal factor being the individual idiosyncrasy against the drug. Yet in cases in which the malaria existed for a long time before the condition occurred it cannot be doubted that the infection or the changes produced by it are very important from an etiologic standpoint. Infections produced by the small as well as the large parasites may lead to quinin hemoglobinuria. Among the latter the quartan parasites seem especially adapted. Vincenzi and Grocco's cases were in connection with quartan affections.

According to Tomaselli's most recent publication, there have been reported 102 cases of quinin hemoglobinuria, to which he adds 12 more. Tomaselli himself saw over 30 cases. In these statistics, only the cases occurring in Italy (with Sicily and Sardinia) and Greece have been taken into consideration. The cases frequently encountered in the literature of blackwater fever, in which hemoglobinuria appeared after the administration of quinin, are not included. We have already expressed ourselves on the question whether there is a genuine blackwater fever or whether all cases are to be looked on as quinin poisoning. Here, therefore, we have only to add that those cases exclusively should be designated quinin hemoglobinuria in which, within a reasonable interval, a paroxysm breaks out every time after the administration of quinin. Cases in which a paroxysm occurs after one administration, but which a few days later bear quinin well, cannot be placed in this category, but are to be looked upon as coincidences. It must not be forgotten that blackwater fever is usually ushered in by a few mild prodromal paroxysms without hemoglobinuria. It can, therefore, readily happen that a dose of quinin is administered before the outbreak of the condition, in which case we can only say that the paroxysm took place in spite of the quinin, not that it was produced by it.

In the typical cases of Tomaselli, Murri, Vincenzi, and others the idiosyncrasy against quinin was preserved for a very long time, even months and years, and could be demonstrated at any moment. Tomaselli observed only isolated cases in which the idiosyncrasy disappeared, and then only a long time after the last malarial infection and after the patients had removed to a region free from malaria. And in these cases it recurred with a new infection.

Murri's case was able to stand, after a year's interval, doses of quinin from 0.10 to 0.50. After its administration there occurred fever, associated with albumin, peptone, and propeptone in the urine, but no hemoglobinuria. Grocco brought his case so far that it could eventually stand large doses (even to 1.5 gm.) subcutaneously, yet on counting the red blood-corpuscles, he always found a cythemolysis, and Vincenzi saw this same case one and one-half years later, when 0.10 quinin would again produce paroxysms.

The paroxysms take place from one to six hours after administration of the quinin. Tomaselli described them as follows: "While rejoicing in perfect health, the patient is suddenly seized by nausea, restlessness, and convulsive twitchings. The skin becomes cool; the pulse small, rapid, and scarcely palpable; the face blanched and accompanied by an expression of suffering. The patient is possessed by a deadly anxiety and not rarely a repugnance to quinin. He complains of pain in the lumbar region, sometimes associated with an internal burning. Thirty minutes to two hours after this stage the temperature rapidly rises to 39° to 41°, according to the severity of the paroxysm. Profuse bilious vomiting sets in; sometimes a serous bilious diarrhea. Urination becomes imperative, and with frequent intermissions a large quantity of blood-stained urine is passed. Salivation, dyspnea, jaundice, severe depression, lipothymia quickly follow. These phenomena usually occur so suddenly that the paroxysm might be termed fulminating, though sometimes this condition is ushered in by a feeling of restlessness, lasting from a few minutes to an hour, which the patient is unable to explain.

"The duration of the fever is variable, depending somewhat on its height. In the majority of cases, after twelve to twenty-four hours, seldom longer, a sudden or gradual fall of temperature takes place, and with it disappear all the symptoms with the exception of the jaundice, which often persists for a short time."

Deviations from this course in one or another direction may occur, yet, taken altogether, the syndrome is pretty constant.

The condition of the blood and the urine is the same as that in hemorrhagic pernicious fever. Grocco found the blood-serum in his case stained red, though shadow-corpuscles were wanting. The isotonicity of the blood was normal. In the urine he found hemoglobin, methemoglobin, large amounts of urobilin, peptone, and propeptone, but a diminution in the phosphates. In mild cases the hemoglobin and albumin were wanting, urobilin only being present.

The duration of the quinin paroxysm is usually shorter than that of true blackwater fever. As soon as the organism gets rid of the quinin the paroxysm ceases (Tomaselli). Paroxysms may be produced by all the preparations of quinin, even when applied locally. The doses which are sufficient are often astonishingly small. Tomaselli saw a case in which 5 centigrams produced the effect.

The hemoglobinuria occurs whether or not a malarial infection exists at the time. Grocco's conjecture, therefore, that we have to do in these cases with a poison excreted by the malarial parasites under the irritation of quinin, is scarcely likely, since to support it we would have to assume that in a number of cases the parasites were concealed in the parenchymatous organs.

It is worthy of remark that quinin, when exhibited in a case of acute malaria, sometimes produces its therapeutic effect, with, simultaneously, a paroxysm of hemoglobinuria. In these cases, therefore, quinin is at the same time beneficial and injurious.

Moreover, the noxious effect may predominate. Tomaselli observed several cases in which complete anuria occurred, followed several days later by uremic symptoms and death. (For the treatment of quinin hemoglobinuria see section on Therapy.)

From what has been stated, therefore, a diagnosis of quinin hemoglobinuria may be made if a paroxysm of hemoglobinuria can be produced every time by the exhibition of quinin (at least, for a period of several months), whether or not malarial parasites happen to be present.

The diagnosis is aided by the patient's history of previous infections and the effect of quinin, to which his attention may have been attracted. The differential diagnosis between quinin poisoning and blackwater fever depends on the principles enunciated on page 322. Still, we may say that no conclusion is to be drawn from a paroxysm occurring after one administration, but only when this effect is repeatedly produced by the smallest doses, both during and apart from an infection.

AMYLOID DEGENERATION.

The occurrence of amyloid degeneration after malaria was demonstrated by Rokitansky. Later experience has shown, however, that it is among the rarities. Budd asserts that he never encountered it, and Frerichs reports only two cases. In Fehr's statistics of 145 cases of amyloid degeneration 4 figure as malarial. In Rosenstein's

43 cases, 4 were after malaria. Axel Key found it repeatedly in the renal vessels. According to Kjelt, it is not rare in Finland after malaria.

Laveran mentions, among his own observations, two cases of amyloid, though both of these were complicated with chronic bronchitis and bronchiectasis. Kelsch and Kiener saw no case. In their work they give only an observation of Grasset's.

DIABETES.

Diabetes Mellitus.—We mentioned, on page 235, that sugar was found in the urine in rare cases of malaria, either during the paroxysm or shortly after it. This glycosuria is usually very transitory. According to Verneuil, however, it sometimes persists so that malaria may be regarded as a cause of diabetes. Verneuil observed altogether six cases of diabetes, all mild, in the histories of which malaria occurred. Girert claims that he has frequently seen, in Panama, glycosuria follow repeated malarial attacks, and that sometimes office-holders must be sent home on account of it.

In opposition stand Le Roy de Méricourt, Laveran, and Grall. The two first insist that diabetes is no more frequent in malarial regions than in other places, and that, therefore, a causal connection between the two is not likely. Grall examined, in Guiana, the urine of almost 500 malarial cachectics for sugar, and found it in but a few cases, and then only in traces. He could not even find an alimentary glycosuria in cachectics after giving them 100 to 150 gm. of syrup. Taken altogether, it is probable that the occurrence of diabetes with malaria is scarcely more than a coincidence.

Diabetes Insipidus.—We have also discussed, on page 234, a postmalarial polyuria. This may be of such a degree and duration as to produce the picture of diabetes insipidus. This persistent polyuria is likewise seen in cachectics (Sydenham).

It must not be forgotten that in some persons quinin has a diuretic effect (Kerner, Schulz). The following case, observed by the author, is a good example of postmalarial diabetes insipidus:

W. J., aged eighteen, draftsman, excepting for a pneumonia in infancy, was always healthy. In March, 1893, he had his first attack of intermittent fever with daily paroxysms. From August, 1893, to April, 1894, he suffered six times from the same disease. In May, 1894, he suffered from tertian fever which continued to July 31, when he was admitted to Nothnagel's clinic in Vienna.

August 1, 1894: Robust, well-developed man, showing a pale, yellowish-brown color. Systolic murmurs over all the orifices of the heart. The spleen extends beyond the border of the ribs about two finger-breadths, is firm, and has a rounded margin. The liver extends beyond the border of the ribs, in the parasternal line, about two finger-breadths. The urine is light yellow, clear, and contains no abnormal constituents.

July 31: 3 P. M.: Had a violent chill which lasted an hour. This was followed by two hours of a hot stage, and eventually a profuse sweat. The temperature rose, about 5 P. M., to 39.5°; at 12 midnight it was 36.9°.

August 1: Apyretic. Amount of urine, 2000 c.c.; sp. gr., 1018.

August 2: Paroxysm like day before yesterday. Urine, 1900 c.c.; sp. gr., 1015.

August 3: No paroxysm. Urine, 3400 c.c.; sp. gr., 1010.

August 4: 1.5 quinin sulph.; no paroxysm. Urine, 1200 c.c.; sp. gr., 1010.

August 5: Quinin as yesterday. No paroxysm. Urine, 2600 c.c.; sp. gr., 1600.

August 6: Quinin 1.0. No paroxysm. Urine, 1000 c.c.; sp. gr., 1012.

August 7: Quinin 1.0. No paroxysm. Urine, 2400 c.c.; sp. gr., 1017.

August 8: Quinin 1.0. No paroxysm. Urine, 2800 c.c.; sp. gr., 1010.

August 9: Quinin, 1.0. No paroxysm. Urine, 4000 c.c.; sp. gr., 1010.

August 10: 3 teaspoons of Levico water. No paroxysm. Urine, 3800 c.c.; sp. gr., 1006.

August 11: 3 teaspoons of Levico water. No paroxysm. Urine, 2800 c.c.; sp. gr., 1010.

August 12: 3 teaspoons of Levico water. No paroxysm. Urine, 900 c.c. (?); sp. gr., 1014.

August 13: 3 teaspoons of Levico water. No paroxysm. Urine, 6300 c.c.; sp. gr., 1010.

August 14: 3 teaspoons of Levico water. No paroxysm. Urine, 5300 c.c.; sp. gr., 1011.

August 15: 3 teaspoons of Levico water. No paroxysm. Urine, 2800 c.c. (?); sp. gr., 1010.

August 16: 3 teaspoons of Levico water. No paroxysm. Urine, 6200 c.c.; sp. gr., 1005.

August 17: 3 teaspoons of Levico water. No paroxysm. Urine, 4300 c.c.; sp. gr., 1010.

August 18: 3 teaspoons of Levico water. No paroxysm. Urine, 6000 c.c.; sp. gr., 1010.

August 19: 3 teaspoons of Levico water. No paroxysm. Urine, 4200 c.c.; sp. gr., 1006.

August 20: 3 teaspoons of Levico water. No paroxysm. Urine, 3500 c.c.; sp. gr., 1009.

Exit.

In this case the polyuria reached a high grade and still continued two weeks after the last fever paroxysm. Whether or not this condition persisted we cannot say. In the future, investigations in this direction would be desirable.

THE RELATION OF MALARIA TO OTHER INFECTIOUS DISEASES.

Malaria and Typhoid.—Boudin's notion that typhoid and malaria locally exclude each other is contradicted by the facts. Over the earth there are a large number of foci in which both diseases are endemic, among which we may mention India, Indo-China, Algeria, and Italy. In a restricted sense they may be said to exclude one another, inasmuch as malaria occurs by preference in the country, typhoid in the cities; yet, as is obvious, this would have little influence in a concrete case.

Moreover, there is in the individual no exclusive opposition to the two diseases. Malaria immunizes against typhoid fever no more than the reverse.

There are numerous reports of autopsies in which the signs of malaria and typhoid fever were found together. Laveran observed several cases of typhoid in persons who had previously suffered from malaria, and still manifested traces of the disease. Malarial cachectics likewise are not at all protected against typhoid.

The most interesting question is, whether an individual can suffer from both diseases at the same time.

Omitting the older observations, as those of Frison, we have others from Kelsch and Kiener, Laveran, Thompson, and Gancel that make a positive answer highly probable.

Laveran several times saw soldiers admitted to the hospital for intermittent fever contract typhoid while there. He further observed that the malarial parasites disappeared from the blood during the typhoid, to reappear after it. Even in the symptoms malaria was scarcely noticeable, the scene being dominated entirely by the typhoid.

Kelsch and Kiener likewise observed cases of typhoid in the course of which malaria manifested itself by producing at intervals irregularities in the fever, marked anemia, and enlargement of the liver. They even endeavored to combine the characters of the two diseases under the name of "proportionate," in Torti's sense.

It is remarkable that the combination of these two diseases has not yet been seen in Italy (Baccelli, Ascoli), although both are endemic and there is no lack of the best observers.

The diagnosis of typhosa proportionata demands the greatest caution, for even when everything is taken into consideration—for instance, the parasitology—mistakes are made both during life and postmortem.

I consider a clinical diagnosis in its old sense to be absolutely unreliable, and, unfortunately, the majority of cases reported so far were diagnosed in this way.

The close clinical resemblance that may exist between subcontinued typhoid malaria and genuine typhoid fever has been mentioned on page 278. Moreover, every physician in practice has seen typhoid fevers that manifest an external resemblance to malaria on account of beginning intermittently with chill and sweating, on account of a continuous remittent course, or on account of septic temperature movements coming on at the close.

Colin, having observed such cases, he considered them at the beginning malaria, but when the continued fever developed, with all the symptoms of typhoid, he concluded that the malaria had been "transformed" into typhoid fever.*

This idea of Colin's, which cannot even be considered in the light of our present knowledge, has not ceased to produce confusion. Fayrer himself, with all his rich experience and his capability of unprejudiced observation, is not free from Colin's influence.† In his clever and careful way he says: ". . . I believe that miasmatic poisoning under certain undefined modifying circumstances may give rise to continued or remittent fever, which becomes practically indistinguishable from specific enteric fever."

Woodward looked at the question from another point of view. He found a number of feverish affections which he could place in the category neither of typhoid nor of malaria, and, supported by clinical observation, he concluded that there was a mixture of the two infections, for which he proposed the name "typhomalarial fever." By this name he intended to describe the simultaneous occurrence of the two diseases in the form of a specific hybrid infection arising from the combined action of both.

If the designation "typhomalarial fever" was always employed in Woodward's sense, there would be no objection to it, though

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* Colin writes ("Traité des maladies épidémiques," p. 807): "C'est sur les malades atteints de rémittente palustre que nous avons vu alors se manifester surtout la fièvre typhoïde, trouvant á l'autopsie d'une part la rate fortement pigmentée de la fièvre pernicieuse, d'autre part les ulcèrations des glandes de Peyer."

† *Loc. cit.*, p. 215.

Woodward himself was not in a position to give anything like convincing proofs that a mixed infection existed in his cases (which occurred during the War of the Rebellion*), and the great majority of cases published since, especially by physicians in the tropics, are also based on inadequate grounds. But it is now more or less customary to describe acute infections which cannot be clinically diagnosed either typhoid or malaria, with the compromise name, "typhomalaria" (Maget).

Naturally, it is impossible to reproach the tropical physicians; on the contrary, we can only feel grateful for their scientific endeavors under the most difficult conditions. The exact diagnosis of a typhomalaria would have its difficulties in a well-supplied clinic; how much more so in a field lazareth in Africa.

Still we must insist that the diagnosis of the combined infection can be assured only when both malarial parasites and typhoid bacilli have been demonstrated, or when, at least, instead of the latter, the Widal reaction is positive.

From the literature that I have seen Vincent is the only one who demonstrated the simultaneous presence of malarial parasites and typhoid bacilli in the same individual. Unfortunately, the original paper is not at my command.

Malaria and Endemic Dysentery.—Since dysentery and malaria are frequently endemic in the same places, it is readily intelligible that an individual might be attacked by both of these protozoan infections at the same time. As a matter of fact, these mixed infections have been frequently observed (see Moursou's extensive treatise).

These two diseases influence each other only inasmuch as the symptoms of dysentery are usually more severe during the fever paroxysm. On this account the association of the dysentery may be overlooked and the case be improperly diagnosed as dysenteric malaria. In the great majority of instances, however, the anamnesis, the microscopic examination of the feces for amebæ, and, in case of death, the localization of the disease in the large intestine, will indicate the diagnosis.

Malaria and Smallpox.—Cases have been repeatedly observed in which patients contracted smallpox while in the hospital for malaria. Laveran found that during the acute stage of variola the malarial parasites disappeared from the blood. Many of the combined cases were very severe. Prince observed a case of obstinate tertian which recovered suddenly after a variola.

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* On working up the "Medical and Surgical History of the War of the Rebellion" Smart found that over 80 per cent. of the cases described as "typhomalaria" were nothing else than remittent malaria (quoted after Rho).

Malaria with scarlatina was observed by Sorbet in one case.

Malaria with relapsing fever was observed by Mamourski in one case. The diagnosis was assured by finding the malarial parasites and spirilla in the blood at the same time. After the exhibition of quinin, the former disappeared, though the latter remained.

Malaria with suppurative infections, like abscess, phlegmon, erysipelas, is not rarely encountered in the typhoid adynamic pernicious fevers as well as in cachectics.

Malaria and Scorbutus.—These two affections are frequently combined during campaigns, when the scorbutus owes its origin to overwork, inadequate shelter, and insufficient or bad food. As to its specific cause, further investigations are necessary.

It is this combination which Haspel described in a masterly way under the name "Fièvre putride scorbutique épidémique." Since then it has been seen during the Crimean war, as well as isolated in special places.

Malaria and beri-beri were observed combined by Däubler.

Malaria and Syphilis.—It has been repeatedly confirmed that syphilis takes on an especially malignant form in malarial cachectics (Moursou, Lepers).

We may add, in regard to all these mixed infections, that the diminution of the resisting power of the organism brought about by the malaria makes it especially suitable for the invasion of a second infection. This double infection is usually severe, and much more threatening than when the two infections are separate.

As to the relations of **lead-poisoning** to malaria, Moursou claims that it creates a predisposition to pernicious attacks, like delirium, epilepsy, hemoglobinuria, cardialgia, etc. We have already stated, in another place, that this writer considers "colique sèche" as lead intoxication, and denies any connection between it and malaria, though we may add that, with few exceptions, his anamnesis failed to show the presence of saturnism.

MALARIA FROM A SURGICAL ASPECT.

From our study so far it is evident that there are numerous occurrences in the course of malaria interesting to the surgeon. I might mention only the gangrene, the neuralgias, the ruptures of the spleen, and the splenic abscesses.

Another direction in which it touches the realm of surgery is that a slumbering malarial infection may be awakened by a trauma. The frequency of these cases has been somewhat exaggerated, yet isolated unmistakable observations have been recorded. Especially wounds of the spleen seem adapted to produce this effect.

The surgical aspect of malaria was taken up particularly by Verneuil, though we must insist that we are not ready to follow him to all his conclusions. We are especially skeptical in relation to the fevers occurring with open wounds which he offers as proofs of his view, as well as in regard to the hemorrhages from operation wounds (for instance, in one case following cancer of the tongue). The source of these is probably to be sought in other things than a reawakened malaria. Only blood examinations can decide this question, and prove in isolated cases whether Verneuil's "Le traumatisme bat le rappel des diathèses" is true, or whether we have to do with new infections or other accidents. Verneuil's views have been completely detailed in a thesis from Taïleb-Oulld Morsly. We will only mention further from this paper that malaria protracts the healing of wounds and the consolidation of fractures.

PATHOLOGIC ANATOMY.

ACUTE MALARIA.

Pigment.—The anatomic characteristic of acute malaria is the melanemia.

Macroscopically this is evident in the grayish-brown to graphite color of certain organs, as the spleen, liver, brain, and kidneys.

Among the older observers who were struck by this abnormal color of the organs and remarked it, though without recognizing its true basis,—*i. e.*, the melanemia,—we may mention Lancisi, Stoll, Bailly, Billard, Mortfaucon, Richard Bright, and, from still later times, Haspel and Annesley. Lancisi noted once a black, pigmented liver, Stoll the same, together with a similarly pigmented brain, and Bright, in his "Reports of Medical Cases," gave a description of a graphite-colored brain.

In regard to the discovery of the malaria pigment by Meckel and Virchow, as well as its physicochemic properties and the views formulated for its origin, we have said sufficient on pages 46 and 231.

Here we intend to consider the distribution of the pigment in the organs. The pigment is free in the blood plasma only in very slight amounts. It is found principally in the parasites (which, on their part, are inclosed in erythrocytes) or in tissue-cells. Among the latter we may mention the leukocytes, the macrophages of the spleen, endothelial cells, marrow-cells, and, more rarely, parenchymatous cells of glandular organs (liver-cells). Among the leukocytes, the polymorphonuclear cells are the most eager scavengers, the lymphocytes playing this rôle but rarely. Yet isolated instances have been observed, as that of Lewellys Barker, in which the lymphocytes had taken up considerable pigment. Eosinophile cells come on this scene only exceptionally.

The distribution of the pigment in the internal organs—as, likewise, the distribution of the parasites—is not, as a rule, uniform. In the section on the etiology of malaria we stated that the quartan parasites are encountered in the peripheral blood in almost the same proportion as in the blood of the internal organs, while the tertian parasites, and, still more, the parasites of the second group, are found in much larger numbers in the latter, and especially in the blood of the spleen, brain, etc.

As demonstrated by Frerichs, the pigment is found in the capillaries rather than in the larger vessels. Again, among the capillaries, the pigmented parasites show a predilection for a certain few, namely, those of the spleen, liver, brain, and not rarely the kidneys. According to Kelsch and Kiener, they are especially numerous in small vessels, where the caliber of the artery goes over suddenly into the narrow caliber of the capillary, thus producing a slowing of the blood-stream, as, for instance, the capillaries of the lungs, the intestinal villi, the appendices epiploicæ, the glomeruli of the kidneys, the dura mater, and the cerebral convolutions. The most common actual sites are the capillaries of the spleen, liver, and brain. Still there are cases in which the distribution deviates from the rule, so that capillary regions which usually show a scanty number of parasites are packed with them, and vice versâ—for instance, Frerichs' case, in which the spleen was free, the liver full of pigment, and numerous others in which the capillaries of the gastro-intestinal mucous membrane were the seats of predilection.

The factors concerned in this varied distribution of the parasites in different cases are at present unknown to us, just as it is not clear why the parasites are not equally numerous throughout the vascular system, where they reproduce, instead of accumulating in certain organs, as if they were breeding-places.

In this respect the malarial parasites behave very differently to dead substances (like powdered glass, cinnabar) introduced into the circulation. These distribute themselves almost uniformly, while the parasites recall the pathogenic bacteria, which, in a similar way, show a predilection for one or another organ.

Let us look at the ordinary distribution of the pigment in the organs. (In this we follow the description of Kelsch and Kiener.)

The Spleen and the Splenic Veins.—When death follows a recent malarial infection, we find in the pulp and the venous sinuses of the spleen numerous large mononuclear and polynuclear cells (macrophages), richly laden with pigment. They frequently contain not only pigment, but also parasites (often together with the infected red blood-corpuscles) in the earlier stages of development, in the stage of segmentation, and even crescents. Not rarely several parasites are found in one cell, in addition to some free pigment or non-infected red blood-corpuscles.

Besides the macrophages, the polynuclear leukocytes and lymphocytes may contain pigment, though in relatively small amounts. In this stage the endothelial cells, the lymph-sheaths of the arteries, the Malpighian bodies, and the connective-tissue stroma are devoid of pigment. Moreover, the arteries contain a much smaller number of pigmented bodies than the veins.

The pigment is found in greatest amount in the splenic vein, where it is seen both in macrophages and in still active parasites.

If a short interval elapses after the acute infection and the patient succumbs to another disease, no parasites will, of course, be found in the circulating blood, and consequently no pigment, while the splenic tissue will be markedly pigmented, and, microscopically, will show this pigment in the pulp, the lymph-sheaths of the arterial vessels, and the Malpighian bodies. The pigment is also more clumped, and is frequently deposited in the form of nests.

Liver, Portal Vein, Hepatic Veins.—In acute cases the pigment is found in macrophages, as well as in parasites within the portal vein and its capillaries. The splenic macrophages are seen especially adhering to the walls of the portal capillaries, which are sometimes occluded by the enormous numbers. In the hepatic veins pigmented parasites occur, but no macrophages. The liver-cells and Glisson's capsule contain no pigment, except when death takes place several days or weeks after the termination of the acute infection.

Bone-marrow.—The large mononuclear marrow-cells are especially pigmented; less so, the smaller ones. In addition the blood capillaries contain pigmented parasites.

In other organs—for instance, the brain, the pia mater, and the choroid—the parasites occur almost exclusively in the vessels. Kelsch and Kiener found, in 40 autopsies, 9 times intense, 17 times mild, melanemia of the vessels of the brain, while the remaining cases showed no or very little pigmentation of this organ. Kelsch and Kiener attribute the rich pigmentation of the brain and pia vessels to the rapid transition of caliber between arteries and capillaries, similar to that which is seen in the pulmonary alveoli, etc.

As stated previously, the capillaries of the pulmonary alveoli, of the intestinal villi, and of the glomeruli are frequently found filled with parasites.

It has been determined by Kelsch and Kiener that in the *lymph-glands* also the pigment is confined to the blood-vessels. An exception to this are the lymph-glands at the hilum of the liver. Here the pigment is accumulated in such enormous amounts, even in the tissue itself (especially in the cortical lymph-follicles), as to be visible to the naked eye. Kelsch rationally assumes that the pigment reaches these glands from the liver by way of the lymph-spaces of Glisson's capsule.

In addition to the black pigment peculiar to malaria, we usually find in the organs considerable amounts of an ocher-colored pigment (hemosiderin). This differs from the first in that it occurs not only in the capillaries, but also, and preferably, in the parenchymatous cells of the liver, the pancreas, the kidneys, and the thyroid gland, as well as in the connective tissue. As is well known, this ocher-colored pigment is encountered in numerous processes associated with the breaking-up of blood-corpuscles—for instance, cirrhosis of the liver, hemoglobinuria, intoxications, stases, etc. It gives the Berlin-blue reaction, and this accounts for the fact, demonstrated by Stieda, that sections of organs of malarial cadavers take on a more or less intense diffuse blue color when treated with ferrocyanid of potassium and hydrochloric acid.

The *blood* postmortem readily shows pigment to the microscope. When the autopsy takes place within a few hours after death, the parasites are found unchanged, but the longer the interval, the more unrecognizable they become. Eventually nothing but the pigment in the leukocytes may be evident. The most satisfactory results are obtained with blood taken from the capillaries of the brain, liver, spleen, or bone-marrow, where both segmentation forms and crescents are found in the largest numbers. (In regard to the other properties of the blood see page 228.)

Spleen.—The spleen is always found enlarged, though to varying degree. Laveran reported, from 12 autopsies of acute pernicious fevers, the average weight as 686 gm. (minimum, 400 gm.; maximum, 850 gm.); Kelsch and Kiener likewise, from 12 cases—an average of 543 gm. (minimum, 300 gm.; maximum, 950 gm.). Since, according to Bollinger, the average weight of the spleen of a healthy adult is 161 gm. in males, 148 gm. in females, the constancy of the enlargement is evident.

The consistence, when no other complication interferes, is decreased, and often to such a degree that, on removal of the organ, it runs to a pap.

The dark-brown, chocolate-like color, varying to deep black, is sometimes diffuse, again in spots. The cut section is dark grayish brown; the non-pigmented Malpighian bodies stand out evidently. The capsule is thin, easily torn, and sometimes shows a perisplenitic exudate.

Microscopically, we find the venous sinuses dilated, sometimes markedly, when they may give rise to hemorrhages. The pulp is covered with red blood-corpuscles, the majority of which are infected. Pigment may be found free, though it is usually inclosed in macrophages.

The macrophages are generally very numerous. Their nuclei stain well, or occasionally not at all, when we may consider the cells degenerated or dead. They often contain, in addition to the parasites and granules of melanin, remains of red blood-corpuscles and ocher-colored pigment; sometimes, too, leukocytes, or even other macrophages. In contrast to the markedly pigmented pulp, the non-pigmented Malpighian bodies are striking. In some cases the spleen is relatively poor in parasites and pigment (Thin). Capillary thrombosis and scattered necrotic foci may be found.

Liver.—The liver is usually enlarged. Its color varies from a steel-gray olive or chocolate color to black. Its weight is greater than the normal average.

Microscopically, we find the capillaries of the portal and hepatic veins, as well as the branches of the hepatic artery, filled with parasites. In the branches of the portal vein we see splenic macrophages, which are sometimes so large that they obstruct the lumina of the capillaries. They are almost never seen in the hepatic veins. The liver-cells are swollen, often contain hemosiderin, sometimes melanin, and, according to Bignami, remains of erythrocytes.

The endothelium of the capillaries is frequently swollen; the lumina thereby narrowed, and sometimes occluded. These endothelial cells, as well as the swollen Kupffer's cells, not rarely contain malarial pigment.

Barker observed in one case isolated areas of necrosis of the liver tissue, probably due to capillary thromboses (by different kinds of leukocytes).

Collections of small cells are not infrequently found in the periportal tissue. These may constitute the point of origin of the subsequent cirrhosis.

In many cases there is a certain amount of hyperemia. To this is attributable the enlargement of the liver, and to it and the infiltration with pigment the increase in weight of the organ.

According to Kelsch and Kiener, the *gall-bladder* is usually found filled with dark-colored bile. There is frequently, too, a large amount of bile in the small intestine. Griesinger observed several times diphtheric processes in the gall-bladder, apparently the result of secondary infection.

Kidneys.—The kidneys rarely show evident pigmentation macroscopically. Still, cases occur in which the cortical substance is dotted with gray points, and the vessels of the pyramids are indicated by gray lines.

The pigmentation is readily recognized microscopically, especially in the glomeruli, where it may be marked. The pigment is found in the glomerular endothelium and in large leukocytes that obstruct more or less the lumina of the vessels.

The endothelium of Bowman's capsule is in places desquamated. The epithelium frequently shows cloudy swelling, and here and there, especially in the convoluted tubules, necrosis. More or less pigment may be found in the uriniferous tubules.

In blackwater fever the kidney changes are marked. The organs are usually enlarged and softer in consistence; in color they are frequently pale and anemic, though again dark red and congested. On the surface are scattered small brownish flakes, the result of diffuse pigmentation of the uriniferous tubules. As first pointed out by Pellerin, the great majority of cases show wedge-shaped, hemorrhagic foci with bases which may be several centimeters square toward the surface and apices toward the medulla. Pellerin observed these foci only in the cortex, and never in the columns of Bertini or in the pyramids. In addition to these recent lesions, he called attention, too, to older cystic cavities situated in the cortex and filled with a dark cloudy fluid. It is doubtful whether these areas, which Pellerin regarded as hemorrhages (apoplexie renale), are not, rather, infarcts. Their form supports this last view, though positive hemorrhages do occur in the pyramids (Kelsch and Kiener, O'Neill).

Microscopically, the kidney epithelium shows a diffuse yellowish and granular pigmentation, with here and there desquamation. Casts, fine granular yellowish pigment, and dark amorphous masses are frequently encountered in the uriniferous tubules. Signs of beginning nephritis are sometimes present.

The renal hemorrhages or infarcts are not exclusively characteristic of blackwater fever. They were observed by Laveran in a case of bilious malaria, with several days' anuria. They vary in number and size, sometimes only a few very small ones being present. Moreover, cases of blackwater fever have been reported without hemorrhages (Wheaton). The relation of these to hemoglobinuria is discussed in the section on Pathogenesis.

Gastro-intestinal Tract.—Macroscopic changes are at most slight, and may be absent.

The most interesting lesions are the occasionally observed swelling of the solitary follicles and Peyer's patches in the ileum and hemorrhagic erosions. The signs of gastro-intestinal catarrh are especially frequent in blackwater fever.

Microscopically, the capillaries of the intestinal villi commonly show more or less pigment.

In one case of choleraic pernicious Bignami found macroscopically intense injection of the stomach and intestinal mucous membrane and numerous punctate hemorrhages; microscopically, enormous numbers of parasites in the capillaries, and wide-spread necrosis of the epithelium. Barker has also found the capillaries of the gastric mucous membrane filled with mononuclear macrophages containing parasites, together with small circumscribed necroses of the mucosa as a result of the occlusion of the vessels by these cells. It is very probable that systematic examination of the mucous membrane of the digestive tract would demonstrate these findings as not uncommon.

The peritoneum rarely manifests alterations. Laveran observed in one case small punctate hemorrhages.

Lungs.—In the lungs, apart from occasional lobular pneumonic areas or infarcts, no macroscopic changes are noticeable. Microscopically, the alveolar capillaries are found filled with infected blood-corpuscles and macrophages.

Heart and Muscles.—According to Colin, Griesinger, and others, the heart muscle is often pale, flabby, and shows fatty degeneration. We have already mentioned Vallin's investigations in reference to the degeneration of the cardiac and voluntary muscles. We may add that Kelsch and Kiener and Laveran attributed the pallor of the myocardium to the general anemia, and were unable to confirm the microscopic findings of Vallin. It is scarcely necessary to state that the vessels of the muscles, similarly to those of the general organism, show red blood-corpuscles inclosing parasites.

Ecchymoses of the myocardium and pericardium have been occasionally observed. The bone-marrow is brownish red, soft, almost diffluent. In the vessels we find numerous adult and sporulating parasites, as well as crescents, outside the vessels; macrophages, frequently showing signs of degeneration. The nucleated erythrocytes seen, sometimes in large numbers, contain no parasites.

Brain and Spinal Cord.—As a result of the attraction which the capillaries of the brain cortex have for the infected erythrocytes the melanosis of this organ is striking. In but few cases of fatal acute malaria is the macroscopic pigmentation wanting. Yet the spinal cord is pale, and shows only here and there grayish-brown lines, marking out the pigment-containing vessels. The two substances of the spinal cord behave similarly to the corresponding ones of the brain.

Microscopically, the pigment-granules in the capillaries of the cortex are sometimes regularly distributed; again, scattered. In the former case we see an extremely pretty outlining of the vessels. This pigment is found in parasites which, on their side, are contained in blood-corpuscles. On cross-section we find the infected erythrocytes along the vessel-walls, the healthy ones in the middle of the stream (Plate VII, Figs. 38 and 39). Pigment is also found in the leukocytes and endothelium. The latter is frequently swollen and gives rise to disturbances of circulation. The swelling of the endothelium of the brain capillaries and the occlusion of their lumina by colorless corpuscles (probably parasites) were discovered by Afanassiew.

The finer vessels are not rarely thrombosed by the infected erythrocytes. This appears to be due to a certain adhesiveness of these blood-corpuscles. More rarely we find other thrombi caused by the accumulation of free pigment, melaniferous leukocytes, and spores.

The parasites found in the brain capillaries are usually advanced in development; in fact, the majority are often in the act of sporulation. Crescents occasionally occur in great numbers. In the larger vessels the younger forms predominate.

Marchiafava and Celli observed in several cases the vessels of the brain filled with non-pigmented parasites. This explains the occurrence of cerebral pernicious fevers without pigmentation of the brain (Plate VII, Fig. 39).

In addition to the melanemia we must not forget the hemorrhages which are frequently found in different varieties of cerebral pernicious fevers. These are usually punctate and sometimes very numerous. According to Bastianelli and Bignami, they are situated about the very small arteries in the white matter of the brain and spinal cord; less commonly, at the border between it and the gray matter. These arterioles are often thrombosed, and show, as a result, degeneration of the endothelium. The extravasated blood-corpuscles never contain parasites. Bastianelli and Bignami assume that the punctate hemorrhages arise by a diapedesis through the injured vessel-walls.

According to Blanc, the majority of hemorrhages are to be found within or near the cortex. This writer also reports an interesting case of apoplectic malaria in which, in addition to numerous capillary hemorrhages, a large subcortical hemorrhage was found that had broken through the cortex. Such hemorrhages, however, seem to be very rare.

Maillot observed two cases with red softening in the lower dorsal portion of the spinal cord. Marchiafava reported in one case with bulbar symptoms degenerative changes in the ganglion-cells of the medulla.

The retina was studied postmortem in ten cases of pernicious fever by Guarnieri. He found the retinal vessels, veins, capillaries, and arteries considerably dilated; the first irregularly, in that normal and dilated areas alternated. The perivascular lymph-spaces were also distended as a result of edema. The capillaries were filled almost exclusively by infected blood-corpuscles, while the veins and arteries showed also healthy erythrocytes. The latter occupied the middle of the vessel, while the infected blood-corpuscles, as seen previously in the cerebral vessels, lay along the walls.

In the choroidal vessels the large number of mononuclear melaniferous phagocytes, in places thrombosing the vessels, was striking.

In two cases small hemorrhages were found, which took in all the external layers of the retina. The extravasated blood-corpuscles were, without exception, healthy, analogously to similar conditions in the brain. The vessel-walls showed only slight alterations. Here and there the capillary endothelium was swollen, fatty degenerated, or necrotic.

In reference to pigmentation of the lymph-glands, we have nothing to add to our former remarks. Enlargement of the glands does not occur.

CHRONIC MALARIA AND CACHEXIA.

The pathologic findings in long-continued cases of malaria are variable and numerous.

It is necessary to differentiate between organic lesions the direct result of the infection, and ones due to complications. We intend to discuss especially the former, but so far as the limits of the work allow, we will not ignore the latter.

It is necessary to differentiate again between the organic changes observed after a long continuous, but not yet terminated, infection, and those which persist after the disease has passed. Since these differ from one another only in the presence and absence of parasites in the circulating blood and organs, a separate discussion is not called for.

The most important alterations in chronic malaria are found in the spleen, liver, and bone-marrow.

Spleen.—The spleen is always considerably enlarged, and usually exceeds a kilometer in weight. Kelsch and Kiener observed, as a maximum in one case, 2625 gm.; Pantioukoff, 3342 gm. According to the latter, chronic splenic tumors are found in 69 per cent. of autopsies in the Caucasus.

The capsule is thickened and in places indurated. This thickening is not uniform, but is irregularly distributed over small areas. In one case I observed the whole capsule calcified. Adhesions to the diaphragm and other neighboring organs are frequent.

By the enlargement the normal form is lost; the consistence is increased; the color becomes a reddish, that sometimes recalls muscle tissue, though while the infection continues it is more grayish brown.

On section, numerous grayish-white lines corresponding to the thickening of the connective-tissue stroma and the vascular sheaths are found. The veins are dilated, sometimes to such an extent that they give the appearance of an angioma. The Malpighian bodies are scarcely or not at all recognizable.

The microscopic picture varies according to the interval which has elapsed since the first infection, for changes are continually occurring which gradually produce, from the soft pigmented, relatively small, acute tumor, the immense hard ague cake. It is impossible for us to follow the gradual phases of this highly interesting process, and we can only refer to the thorough work of Bignami, to which we have had frequent recourse in the following.

Shortly after the cessation of the infection, the most important histologic factors are: A marked diminution in the hyperemia; miliary necrotic areas and intense hyperplastic processes in the pulp and sometimes in the follicles. The arrangement of the pigment changes, in that it collects in heaps in the pulp, concentrating itself about the vessels, and in the connective-tissue septa.

In later stages the pigment is found only in the perivascular lymph-spaces, and gradually a larger portion of it is resorbed by the spleen. The macrophages, which, in the acute enlargement, were the carriers of the pigment, have disappeared, probably as the result of degeneration, and the pigment is now extracellular. Later on the pigment disappears entirely.

The necrotic areas are gradually resorbed, while the hypertrophy of the septa, the dilatation of the vessels, and the lessening of the pulp become more and more conspicuous. The follicles undergo fibroid degeneration and become eventually unrecognizable. The final ague cake is made up principally of thickened stroma and dilated vessels; the pulp-cells and follicles are reduced to a minimum, and the physiologic function has almost disappeared.

Liver.—The liver is enlarged and may reach a weight of three or four kilos. Its surface is smooth; its consistence, increased. The capsule is frequently thickened. The cut section varies according to the time that has elapsed since the infection. Regularly pigmented during the acute infection, we see, in the course of time, the pigment lines becomes arranged perilobularly, with the production of a very pretty network.

Shortly after the infection we find microscopically the following (Bignami): The capillaries are devoid of parasites, the endovascular macrophages have disappeared, and the pigment is exclusively in the endothelial and Kupffer's cells. The necrotic parts of the lobules atrophy, and the vessels dilate in consequence.

Later on the lobules get rid of the pigment by means of mononuclear and polymorphonuclear leukocytes, which carry it to the periphery. At the same time regenerative changes are occurring in the liver-cells.

As a result of the atrophy and regeneration we find here false angiomata and lymph-cysts, there, enormously large lobules. The pigment is carried from the vessels by leukocytes and deposited in the perivascular lymph-spaces. The perilobular connective tissue becomes hyperplastic.

Eventually, therefore, we have a large hard liver of reddish color, which, on section, shows conspicuously the granular-looking lobules surrounded by their connective-tissue stroma. The vessels are dilated; the amount of blood in the organ is increased, and the pigment is no longer visible.

According to Kelsch and Kiener, a few months after the termination of an infection no pigment can be found in the organs. Bignami likewise observed that after three to four months the greatest portion of the pigment had disappeared.

In addition to the three forms of parenchymatous nodular hepatitis (with hyperemia, with cirrhosis, and with adenoma) Kelsch and Kiener differentiate an insular cirrhosis with nodular hepatitis, an insular cirrhosis with diffuse parenchymatous hepatitis, and an annular cirrhosis with parenchymatous hepatitis. Though these cirrhoses have been carefully described by Kelsch and Kiener, we refrain from further details, since they have not, as yet, been generally accepted.

Marchiafava and, according to him, Bignami deny, as we have previously stated, that cirrhosis develops as a result of malaria. They admit a perilobular increase of connective tissue about the individual lobules, but assert, at the same time, that the branches of the portal vein are not only not destroyed, but further developed, while in Læennec's cirrhosis the connective tissue surrounds several lobules at a time and produces strangulation of the portal vessels. Moreover, the liver-cells themselves show differences.

According to their description, also, the enlargement cannot be identified with hypertrophic cirrhosis.

Atrophy of the liver in cachectics is not infrequent. Frerichs affirms that it is not infrequently the result of occlusion of numerous liver capillaries by pigment-cells. Bignami observed it once as a consequence of thrombosis of the portal vein.

The atrophic liver is small and of increased consistence. Its surface is smooth or finely granular; its capsule, thickened. The structural alterations are usually not marked and likewise not constant.

We have already spoken of the occasional occurrence of amyloid degeneration and have nothing further to add.

The **bone-marrow** at the upper and lower extremities of long bones is red and of increased consistence. Microscopically (Bignami) the fat has disappeared and is replaced by proliferated marrow-cells and new blood-vessels. The large and small mononuclear myelocytes are increased, and many show signs of degeneration. In addition there are numerous nucleated red blood-corpuscles of normal size (normoblasts), and a few gigantoblasts or megaloblasts. The endothelium of the vessels is swollen, and the vessel-walls and the stroma are thickened. The pigment disappears from the bone-marrow much sooner than from the other organs.

The **inflammatory renal changes** found in chronic malaria, both antemortem and postmortem, are variable. Kelsch and Kiener describe among the commonest glomerulonephritis with a tendency to secondary contraction, and a large kidney with peculiar white specks. Rem-Picci considers a chronic contracted kidney as a result of malaria doubtful. This authority frequently saw amyloid degeneration of the kidneys. It is impossible to go further into histologic details.

Lungs.—The lesions in the lungs produced by complicating bronchopneumonia, infarcts, lobar pneumonia, chronic indurative pneumonia, gangrene, etc., correspond in general to the same processes in the cachexia, and we will, therefore, refrain from another description.

The **intestinal tract,** apart from the dysentery which frequently acts as a complication, shows nothing peculiar.

The **peritoneal cavity** is frequently filled with transudate. Peritoneal adhesions of greater or less extent proceeding from the perisplenitis are encountered.

The **circulatory apparatus** occasionally participates, with dilatation and hypertrophy of the heart. Aside from complications, no essential changes have been recognized in the **central nervous system.**

THE PATHOGENESIS OF MALARIA: ITS POSITION IN PATHOLOGY.

From the standpoint of general pathology, malaria is an infectious disease of man caused by protozoa, which attack the blood, or, more accurately, the red blood-corpuscles. If, on the basis of our present knowledge, we were to give malaria a rational name, this would probably be "erythrocytonosis protozoïca." As an infection limited to the erythrocytes, malaria occupies in human pathology a unique position. So far no second parasitic disease of the red blood-corpuscles of man has been recognized. Yet the interesting discoveries of Gaule, Danilewsky, and others in the lower animals have proved that such infections are not confined to man.

Aside from the infection of special cells, malaria is of further general interest in that it is the first protozoan infection of the human organism determined with certainty.

On account of the interdependence of all cells in an organism, it could not be expected that the disease changes in the blood-corpuscles would be without influence on the remaining cells. As a matter of fact, the examination of the peripheral blood itself would disprove such an idea. This shows the circulating leukocytes containing black pigment, the product of digestion of the hemoglobin in the bodies of the parasites. This pigment may be introduced into the leukocytes in three ways—namely, the leukocytes acting as phagocytes may take up pigment rests that have become free by segmentation of the parasite; second, they may take up entire pigmented parasites, or, finally, the parasites may force their way in a hostile manner into the leukocytes.

Anatomic investigation shows further and greater effects. Pigment and parasites are found in larger and smaller mononuclear and polynuclear cells in the spleen, liver, bone-marrow, and lungs, and pigment alone in the vascular endothelium of different organs and Kupffer's cells in the liver.

Even more important is the faculty manifested by the infected blood-corpuscles of adhering to the vessel-walls and accumulating in certain capillaries, so as occasionally to obstruct them.

The question that at once suggests itself is, How does the organism eliminate the malarial pigment?

A great part seems to be absorbed by the leukocytes, especially the macrophages; the rest is deposited by these cells in the neighborhood of perivascular lymph-sheaths, and in these lymph-sheaths the pigment is eventually found.

To the lymph apparently falls the work of removing it further. How it does this is not yet very clear. The lymph possibly dissolves a part, though some is undoubtedly deposited in the lymph-glands, as is evident in the case of those neighboring the liver. These glands perhaps finish the work.

It is questionable if the parenchymatous cells participate at all in the absorption of the pigment. True, we sometimes find liver-cells containing pigment, but whether or not they are able to transform it into bile we cannot at present say.

In addition to the black pigment, which, as the product of the parasite, is pathognomonic for malaria, there is the ocher-colored pigment to account for.

In contrast to the malarial pigment which is elaborated in the peripheral blood, the ocher-colored pigment takes its origin in the tissues. It is found especially in the liver-cells, the spleen, the bone-marrow, the kidneys, the pia, the thyroid gland, and the pancreas. It is observed only exceptionally in the vascular endothelium and circulating leukocytes.

This ocher-colored pigment is a derivative of hemoglobin, and originates from the destruction of red blood-corpuscles, which are not completely consumed by their parasites. This is less true of the tertian and quartan parasites than of the parasites of the second group, which segment at a time when they scarcely half fill the corpuscle, so that considerable amounts of hemoglobin or corpuscular débris are thrown into the plasma. Another source of hemolysis is probably found in the necrosis and fragmentation of non-infected erythrocytes, due to the action of the toxin.

The hemoglobinuria proves that under circumstances the hemolysis may be enormous, though we are not yet in a position to explain the conditions responsible for it.

Whether the fragments of the erythrocytes are taken up as such by the parenchymatous cells and transformed into this ocher-colored pigment, or whether only the hemoglobin of these fragments infiltrates the cells in a dissolved condition and is there precipitated in this form, is a question which, in our opinion, may be answered by the assertion that both probably occur. The further fate of this pigment is only partially known.

It is very probable that the liver-cells elaborate their portion into bile, which would thus explain the frequently observed polycholia.

How the other organs act toward it is not fully understood. Some of them—the spleen—seem to send it on to the liver. Whether it can be elaborated into urobilin in the places where it occurs outside the liver, as some authorities assume, must be considered questionable.

In contrast to the disturbances produced by the pigment, which, as we have seen, affect almost every cell in the body, the *necrotic processes* in the parenchymatous organs play a secondary rôle. The greater part of these are the result of capillary thromboses, though some must be attributed to the effect of toxins. The elimination of these necroses is usually brought about in the same way as in other infectious diseases.

In regard to the *connective-tissue overgrowth* (splenic tumor, cirrhosis) that is seen as a remnant, it is impossible to say whether it is produced by "irritation" of the pigment or is the result of an equalization of equilibrium in the tissue following the necrosis of parenchymatous cells.

Up to a relatively short time ago the *disease symptoms* were a problem, the solution of which had occupied the minds of pathologists of all ages. But Laveran's discovery and the investigations of other observers have so thoroughly explained them that malaria may now be reckoned among these diseases, the pathogenesis of which has, to a great extent, been scientifically determined.

If we analyze the most important symptoms with reference to their origin, our attention is attracted to the triad, melanemia, anemia, and fever.

In regard to the *melanemia*, we have nothing to add to what has already been said in the previous sections. The origin of the pigment in the bodies of the parasites as an end-product of the hemoglobin digested by the protozoa, has been absolutely determined and needs no further proof.

The second symptom, the anemia, may also be regarded as explained.

The degree of the *anemia* depends, on the one hand, on the number of the parasites and the rapidity with which they increase; on the other, on the activity of the blood-making organs. The latter is never sufficient to make good the loss with the rapidity of its occurrence; a certain degree of anemia, therefore, is never lacking. The high degree that may occasionally be reached has been repeatedly discussed in the clinical description.

The third principal symptom—the *fever* or the fever paroxysm in its typical and atypical forms—has likewise been explained and satisfactorily, even though not so clearly and simply as the melanemia and anemia.

Golgi's demonstration of the coincidence of the fever paroxysm with the segmentation of the quartan and tertian parasites; Marchiafava and Celli's demonstration of the same for the quotidian parasites; and Marchiafava and Bignami's for the malignant tertian parasites, have divested the intermittent fever paroxysm, with its periodic recurrence, of the mysticism surrounding it, by referring it to a simple biologic fact. This biologic fact is the cycle of development of the parasites occurring at the time in the blood.

Turning to the fever paroxysm itself, with its three separate stages, we find that it sets in with the segmentation of a generation of parasites.

The association of this segmentation with the fever paroxysm in the way of cause and effect was neither an unjustifiable nor too bold an employment of the usually condemned argument *post hoc ergo propter hoc.*

Golgi described the process as follows: As a result of the sporulation an enormous number of spores, together with substances elaborated in the parasites and probably poisonous to the organism, are thrown into the blood and produce the paroxysm.

That, exceptionally, isolated segmentation forms may be found in the blood apart from a paroxysm is no argument against this standpoint, for undoubtedly a certain quantity of the injurious agent is necessary to produce symptoms.

The fact that the parasites exist in the blood in generations which show individual members of almost exactly the same age makes this theory of the paroxysm probable.

How it happens that such an innumerable number of parasites as are often present in the blood are of the same age is unknown, though we have a hypothesis that probably approaches the truth.

It is assumed that infection results only when the organisms are in a very definite stage of development. Let us suppose, for the moment, that spores introduced either by mosquitos or by aspiration into the lungs produce the infection. If a certain number of these gain entrance, a basis is at once formed for the evolution of a generation, all the members of which will be of the same age. It is somewhat similar to several human beings of the same age marrying and begetting children simultaneously. It is evident that in the continuation of this parallelism in the reproduction a large number of individuals of the same age will eventually result. Moreover, in the case of the malarial parasites it is much more sure, since their time of evolution is very definite, namely, the quotidian parasite twenty-four, the tertian two times twenty-four, and the quartan three times twenty-four, hours. Within a short time, therefore, large numbers of families of the same age will be produced from a relatively small number of micro-organisms.

Still, we must insist again that this similarity in age of the different individuals is not absolute. If all the parasites which we reckon as belonging to the one generation were the same age to the minute, and if this entire host would segmentate at a given moment and throw off their spores, then the blood-picture would correspond exactly with the outline, but, as a matter of fact, the parasites of the same generation show differences of one to several hours. The struggle for existence is evidently a factor capable of influencing the duration of evolution. In spite of the slight differences in age it is necessary to reckon all these individuals to one generation.

The fact that the individuals of one generation do not sporulate at the same moment, but after one another at short intervals, produces its own clinical feature in that the paroxysm does not ordinarily last only a few moments, but several hours—even half a day and more. In relation to this, we previously wrote*: "If the innumerable sporulation forms, similarly to a volley of a large number of guns, would burst in a moment and throw their contents into the blood-stream, it is very likely that a much shorter but also much more violent paroxysm would be the result, but, as it actually is, the sporulation takes place after the manner of a rapid fire, and continues the fever paroxysm through a series of hours." That toxic substances are set free at the time of the rupture has not yet been fully demonstrated, though the assumption can scarcely be wrong. True, Roque and Lemoine found that the toxicity of the urine excreted after a paroxysm was higher than normally, and Queirolo showed that the sweat of malarial patients, similarly to that of other acute infectious diseases, was poisonous to rabbits; yet these experiments are by no means convincing.

* *Loc. cit.*, p. 110.

The occurrence of degeneration in the nervous centers and the kidney epithelium (Marchiafava and Bignami), independently of thrombosis of vessels, favors the view that a poison is present in the blood.

It is this hypothetic toxin which is made responsible for the paroxysm through its action on the vasomotor and heat-regulating centers. This responsibility is supported by striking analogies from general pathology. We may recall, for instance, the septic and pyemic fever paroxysms. These are nothing else than the reaction of the organism to the toxin of the bacteria. We must concede that these poisons show a certain similarity in their physiologic action to the malarial toxin, although we have so far no satisfactory explanation for the irregularly recurring fever paroxysms in these cases, while the biologic evolution of the parasite explains the periodicity of the malarial paroxysm.

We cannot deny that Laveran, to whom we owe so much in the etiology of malaria, both in reference to the genesis of the paroxysms and of the fever generally, takes quite another point of view. Laveran rejects Golgi's law as to the dependence of the paroxysm on the segmentation of the parasites, and seeks the cause of the periodic fever in the attacked organism itself. This standpoint of Laveran's depends on the fact that he recognizes only one pleomorphous parasite, not several species, and he cannot, therefore, attribute the different types of fever to the different species.

Laveran ascribes the intermittence of the paroxysms to an intermittent activity of the phagocytes. In order to explain the different types he presupposes a greater or less "activity" on the part of the parasites in different countries, together with a difference in the reaction of the human organism.

Although we have stated our opinion in reference to the different species of parasites in another section, we wish again to dispute Laveran's view and refer to our former utterances, adding that we consider the differentiation into species as incontrovertible and the intermittence of the fever as undoubtedly grounded on the duration of the evolution of the parasites.

Turning to the individual types, we find that—a quartan fever is without exception produced by quartan parasites; a tertian fever is without exception produced by tertian parasites (these may be either the tertian parasites of the first group, or the malignant tertian parasites of the second group); a quotidian fever is produced by one generation of quotidian parasites (of the second group), or two generations of tertian parasites, or, finally, three generations of quartan parasites.* In the first case we have to do with a genuine quotidian fever; in the other two we may rationally speak of a double tertian or a triple quartan.

This is by no means a new idea; even the most ancient writers, like Celsus, realized these combinations. Their attention was called to them by the varying intensity of corresponding paroxysms, or by the differences in time in their appearance (for instance, one paroxysm in the morning, another in the afternoon).

The following scheme will serve to show these combinations concretely. The brackets connect the numbers belonging to one another, and designate thereby the type. The numbers themselves indicate the days on which fever paroxysms occurred, while the ciphers mark the intervening days when no paroxysm took place:

1001001001, etc. . . . . Simple quartan.
10101010101, etc. . . . . Simple tertian.
1 1 1 1 1 1 1 1 1 1, etc. . . . . Simple quotidian.
1212121212, etc. . . . . Double tertian (false quotidian).
1231231231, etc. . . . . Triple quartan (false quotidian).
1201201 2012, etc. . . . . Double quartan.

In regard to the intermittent fever with long interval, for instance, septan and over, we have already stated that these, from the standpoint of present knowledge, must be considered relapses. They usually occur in individuals who have suffered a long time from malaria, and who, at certain intervals, take quinin, but in insufficient amounts. On this account micro-organisms are left in the blood, which, after a gradual increase, become capable of producing a paroxysm. In cases which took no febrifuge we may assume that such an enormous number of parasites succumb during the paroxysm as to require some time before an active generation develops.

So far we have no knowledge of a species of parasites having a period of evolution over three times twenty-four hours. The possibility that such a species exists cannot be denied, though the probability is very slight. Experience shows that the fevers with long intervals ordinarily follow fevers of quotidian or tertian type; it is very likely, therefore, that our explanation is a very close approach to the correct one.

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* See Tab. II, p. 60.

We have still to discuss the subintrant, the continued, and the irregularly remittent fevers. The common feature in their genesis is the presence, in the blood, of several generations of the same or different species of parasites. It is evident that under these circumstances segmentation may proceed almost continuously, and regular intermissions or even intermissions at all fail to occur.

In the very great majority of these cases we have to do with multiple infection with parasites of the second group, especially the malignant tertian parasites. Marchiafava and Bignami have shown that there are usually not more than two generations.

With one single generation of these parasites the fever paroxysm is usually long; it is easy, therefore, to understand that a double generation would produce a continued or subintrant fever.

The parasites of the first group are much more rarely in sufficient generations to produce these fevers. When, as frequently happens, generations of the first and second groups occur in the blood at the same time, the character of the fever becomes irregular.

The difference between subintrant and continued is only one of degree. In the first case, a slight fall of temperature marks the boundary between two paroxysms, while in the second case the transition is unnoticeable. Parasitologically, in the subintrant there is a short interval in segmentation, so that the parasites can be divided into two (or more) generations; in the continued there is a continuous segmentation, so that a division into generations is impossible.

Infections caused by parasites of the second group very frequently show at the beginning a continued fever. Only after the course of several days, and then usually under the influence of quinin, does this continued change into an intermittent. I have occasionally seen the same thing occur in infections of the first group, though this is relatively rare.

In subtropical and tropical regions, in the midst of the chief foci of severe infection, it is a daily occurrence to see the primary infection begin as a continued or remittent and after a few days change to intermittent.

We are not at present sufficiently advanced to explain this occurrence in a parasitologic way. Accurate blood-examinations of the initial continued, as it has been designated, will probably show the reason for it. In several observations the peripheral blood has been found during the initial continued poor in parasites.

Turning back once more, we wish again to insist that the fever paroxysm is the result of the action of the poison elaborated by the parasites on the vasomotor centers.

In the older speculations the two factors that constitute the basis of the paroxysm were sometimes properly comprehended, though again too much predominance was given to one.

Torti attributed the intermittence to a poison which, from time to time, contaminated the blood.* Bailly asserted " . . . L'intermittence est une disposition physiologique consistant dans l'excitation alternative des fonctions des deux systèmes nerveux, abdominal et cérébral. . . " In the same way as Bailly and Van Swieten, Trousseau comprehended the question. He explained malaria as a "neurosis." Griesinger energetically contradicted this opinion, and with astonishing acumen insisted: "The cause of the periodicity of the fever cannot, therefore, be referred, as has frequently been done, to a predisposition of the nervous system to rhythmical vital phenomena. On the contrary, from the present state of our knowledge of the production of temperature (though this is very incomplete) it must be attributed to some periodic occurrence in the blood associated with elevation of temperature."

The *severity of the paroxysms* is, according to Golgi, in exact proportion to the number of parasites. Yet the peripheral blood by no means gives a proper idea of the number, since accumulations in the internal organs are very common. Moreover, the specific virulence of the parasites, as well as the power of reaction on the part of the individual, also comes into consideration.

The postmalarial secondary fever which is sometimes observed in cachectics rarely after primary infections is not very clear in its pathogenesis. It is usually slight, extends over days or possibly weeks, shows a negative blood examination, and does not react to quinin. It is possible that the anatomic lesions produced in the parenchymatous organs are responsible for it.

The *change of type*, a frequent phenomenon in malaria, for which previously there was no explanation, is at present attributed to the increase or diminution of the generations.

The manner in which the generations increase or decrease, though easily comprehended in some cases, is a problem in many. It is sometimes possible to distinguish in the blood two generations of parasites—one in such small numbers as to be incapable of causing paroxysms; the other in large numbers and producing them. The first generation becomes stronger from day to day until at length capable of producing first mild, then severer, paroxysms. Whether such a generation arises through a second infection or by the separation, within the organism, of individual members from the one generation, we cannot say.

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* *Loc. cit.*, Lib. i, Cap. viii.

A change of type by a falling-out of a series of paroxysms is the result of the death of a single generation of parasites. This disappearance of a whole generation or the greater part of it may occur either under the influence of therapy or spontaneously. In this way we frequently see a simple tertian develop from a double tertian. That quinin may kill a single generation and spare a second is due to the parasites possessing a different susceptibility for the drug, according to their age.

It was previously thought that the change of type occurred arbitrarily—in other words, that from one type any other might develop. The faculty of anticipation and postponement was employed to construct an outline showing the transition of one type into others.

The actual condition, however, is very different. The change of type takes place only under very strict rules, and anticipation and postponement scarcely come into consideration, or at most only incidentally. Naturally, these rules apply only when the infection is simple—that is, when only one species of parasites is in the blood, and a subsequent infection from the external world is excluded. Under these circumstances a continued, a tertian, or a double or simple quartan may develop from a quotidian; a quotidian or a continued from a tertian; a double quartan, a quotidian, or a continued from a quartan, but a tertian never from a quartan, or vice versâ.

A difficult question is, Why in multiple infection do the parasites usually show a difference in age of about twenty-four hours, or two times twenty-four hours? in other words, why do the paroxysms of two generations fall about the same time in the day? True, this rule has many exceptions, and it occasionally happens that in double tertian, for instance, one paroxysm occurs in the morning and the other in the afternoon; yet the occurrence of the paroxysms at the same time on different days in such a great majority of cases furnishes food for reflection, because it is at present inexplicable.

Anticipation and postponement of the paroxysm are produced by the parasites developing more rapidly or more slowly than is ordinarily the rule.

For the present we must regard it as a coincidence—even though it possibly is not—that the duration of evolution of the malarial parasites is twenty-four hours or a multiple of it, or, in other words, that it keeps step with our calendar day. Yet a generation may depart from this astronomic cycle and develop in a more (postponement) or less (anticipation) number of hours.

The more rapid development may depend either on an increased virulence of the parasites or a lessened resisting power on the part of the individual. Postponement is almost always the result of a retarded evolution produced by medication. The occurrence of the paroxysm at a later time is frequently observed after the first administration of quinin.

Relapses occur when some micro-organisms fail to fall victims to the quinin, and later develop into sufficient numbers to produce paroxysms. It cannot be doubted that in the great majority of cases relapses are attributable to insufficient treatment, just as is the case in acute articular rheumatism.

We need only call attention to the similar duration of the intervals after which the majority of relapses occur and those which ordinarily constitute the period of incubation. The connection between these two facts need scarcely be mentioned. Still it sometimes happens that relapses occur in spite of sufficient and proper treatment. This would seem to indicate that there are parasites which possess a very high power of resistance to quinin. This conclusion is especially true of the crescents, which are absolutely refractory to quinin. The obstinate relapsing of estivo-autumnal fever is thereby explained.

In fevers of the first group, not omitting quartan, we have no knowledge of refractory forms. Nevertheless it is possible that there are such forms, and likewise possible that Bignami's view may be the correct one.

Bignami assumes that the spores contained in the macrophages may become again capable of development after degeneration of their hosts. The inclosed spores are, therefore, to be regarded as latent parasites, capable, under circumstances, of reproduction.

It is possible, too, that, like certain bacteria, the malarial parasites are protected in the *spleen*. It is only necessary to recall cases in which trauma, electrization, or massage of the spleen called forth paroxysms. In those cases it may be that the latent parasites are forced from the spleen into the circulation, when paroxysms result as a consequence.

Though the relapses occurring within several weeks may be so explained, the problem remains unsolved how paroxysms can occur months and years after a single infection. Still we must say that further investigations are wanting to prove absolutely that there are such relapses without a renewal of infection.

The acute enlargement of the spleen which constitutes an almost constant symptom of malaria is attributable to different factors, as intense hyperemia, the deposition of large amounts of black and ocher-colored pigment and of necrotic blood-corpuscles, the invasion of parasites in all stages of development, in macrophages, in endothelial cells, and free in the pulp, etc. Moreover, a large number of the infected erythrocytes from the circulation are retained in the spleen, and it is probable that a further increase in parasites takes place there. Finally, the occlusion of the portal capillaries in the liver by pigmented macrophages, first observed by Frerichs, may exercise an influence by the consequent stasis (Bignami).

The phenomena coming into consideration in chronic tumor of the spleen have been sufficiently discussed in the section on Pathologic Anatomy.

Whether the spleen plays a more inimical or protective rôle toward the parasites is uncertain. It is undoubtedly true that it frequently constitutes a center of location for them; in fact, there are cases in which the peripheral blood is very poor in parasites, when puncture of the spleen shows the presence of numbers. The numerous macrophages filled with parasites would speak for the inimical rôle; the occurrence of enormous numbers of actively developing parasites, for the protective one.

The fact seems to be determined that malaria does not, at least, run a severer course after removal of the spleen than before (Tizzoni, Massopust).

The obstruction of the capillary circulation constitutes the important cause of the functional disturbances in the *central nervous system.* Planer made the pigment thromboses of the brain capillaries responsible for the different symptoms of cerebral pernicious fever. Frerichs agreed in part with Planer's conclusion, but introduced other considerations. Though he frequently observed pigment thromboses of the brain capillaries, as well as occlusion by white thrombi, he insisted that too much stress should not be laid on them, on account of the rich collateral circulation. He likewise affirmed that he had more than once seen markedly pigmented brains without cerebral symptoms during life, and that among 28 cases of cerebral pernicious fever, the pigmentation was entirely lacking in 6. On the whole, Frerichs seemed more inclined to think that it was chemic products resulting from the destruction of the red blood-corpuscles that produced the cerebral symptoms.

The older observers recognized not only the thromboses of the vessels, but also the capillary hemorrhages, the result of them (Meckel, Planer), and Frerichs has even reported a large meningeal hemorrhage. Our views to-day in regard to the origin of the cerebral disturbances differ in but few points from those of previous authorities.

Laveran, Marchiafava, and Celli demonstrated that we have not to do with pigment thromboses, but with obstruction of the vessels by infected erythrocytes. The tendency of these erythrocytes to adhere to the walls of the smaller vessels has already been spoken of, and the obstruction is aided by swelling of the capillary endothelium.

In the majority of cases, therefore, the thrombosis is produced not by a dead mass, like pigment, but by living parasites inclosed in blood-corpuscles. Only occasionally do we meet true pigment thrombi or ones that are made up of melaniferous leukocytes, free parasites, or free spores (Marchiafava and Bignami). This origin of the thrombi makes it intelligible how severe cerebral disturbances may come and go with surprising rapidity. The obstruction to the circulation is of such a kind that it may be removed even as quickly as it develops.

In case of cerebral disturbances without melanemia of the brain the existence of non-pigmented parasites must not be forgotten. These have been repeatedly found in large numbers in the brain (Marchiafava and Celli). They may be either parasites that elaborate no pigment or young forms of pigment-producing parasites.

The transitory disturbances of the brain, therefore, find their explanation in the lessened amount of blood as a result of accumulations of infected erythrocytes; the long-continued functional disturbances in the capillary and larger hemorrhages and in the derangements of nutrition produced by the interruption of the circulation. Whether a toxin is also to be taken into consideration can only be conjectured, though, judging from the peripheral neuritides repeatedly observed after malaria, this is very probable.

Some of the *gastro-intestinal disturbances*, like vomiting and profuse diarrhea, are undoubtedly best explained by the accumulation of erythrocytes in the capillaries of the gastro-intestinal mucous membrane. It has been stated in a previous section that these accumulations may lead, as in the brain, to thromboses, to capillary hemorrhages, and to necroses.

The flooding of the duodenum with bile, as is not infrequent in malaria, may likewise provoke these functional disturbances, especially the bilious vomiting.

In addition to these, there are doubtless other factors not yet fully understood. The vomiting during the chill, for instance, is probably nervous in character. To what extent toxins come into play we cannot at present say.

The sensory disturbances, like cardialgia and colique sèche, are not yet susceptible to explanation.

The intermittent hemorrhages from the intestine, stomach, and the esophagus, as well as the acute ascites, have been attributed by Frerichs to occlusion of the portal capillaries by pigment.

The enlargement of the liver is due to hyperemia, swelling of the endothelial and parenchymatous cells, and the invasion of pigmented macrophages. The atrophy of the liver is, according to Frerichs, due to occlusion of the portal capillaries; according to Bignami, to a thrombosis of the portal vein. Still, the most frequent cause seems to be general marasmus.

The icterus, which may vary from very slight to most intense, is at present regarded as polycholic in character. During the infection large quantities of corpuscular débris are brought to the liver for further reduction. The product of this reduction is bile. These corpuscular fragments consist in part of infected erythrocytes, but in part, too, of necrotic erythrocytes which undergo degeneration as a result probably of the toxin.

It is likely that the hemoglobin of these fragments comes to the liver in a soluble condition, even though, so far as I know, no one has demonstrated it in the blood-plasma. In three cases which I investigated I obtained a negative result; nevertheless, many circumstances go to indicate that the corpuscular débris is incapable of holding the hemoglobin. This is apparent microscopically after the excapsulation of the parasite, when we usually see a completely colorless shadow, the remains of the hemoglobin having disappeared.

Whether the melanin is further reduced by the liver cannot be stated with certainty. This is, at least, true, that a larger amount of raw material than normally is brought to the liver, and that from this polycholia results. The polycholia is frequently expressed by bilious vomiting and bilious evacuations. The icterus may be compared to that which occasionally accompanies other infectious diseases, like sepsis, pneumonia, etc., with this difference, that in malaria it has a more legitimate place.

If the destruction of blood-corpuscles occurs rapidly and in great numbers, so that Ponfick's postulate in relation to the destruction of a sixth is fulfilled, in addition to icterus, hemoglobinuria is seen.

We stated before that we attribute the hemoglobinuria to a solution of the blood-corpuscles within the vessels. Pellarin's view that the hemoglobinuria is produced by renal hemorrhages has been found wanting, inasmuch as there are cases in which no renal hemorrhages were found and others in which it was possible to demonstrate the hemolysis in the peripheral blood.

Karamitsas was probably correct when he assumed that Pellarin's renal hemorrhages were infarcts the result of thromboses by shadow-corpuscles. Still, the final cause of the hemolysis in blackwater fever or in postmalarial quinin intoxication is unknown. For the hypotheses in regard to it we refer to the corresponding sections.

The anuria and uremia of blackwater fever are explained by the occlusion of renal vessels by shadow-corpuscles and granular detritus.

The latent fevers still show much that is problematic. The difficulty lies in the absence or insignificance of the fever. This is probably due to the small number of parasites ordinarily found in these conditions. Nevertheless, there is some question whether they may not be due to a changed reaction on the part of the organism, a certain tolerance of the vasomotor centers toward the virus. We know, for instance, that latent fevers usually occur after repeated typical attacks. It is, therefore, possible that the centers may have acquired a certain insensibility to the poison. The positive symptoms of the latent fevers are commonly such as are manifested by these persons under other circumstances. Further than this we cannot follow the pathogenesis.

In the preceding we have endeavored to show the pathogenesis of the most important symptoms. We refrain from analyzing the occasionally occurring symptoms, since it would carry us too far and we would often be forced into the realm of pure speculation. This is especially true of the complications which we have reviewed in the clinical part as far as their pathogenesis is known.

DIAGNOSIS.

Malaria is diagnosed from the clinical symptoms, the action of quinin, and the blood examination.

The clinical symptoms are often sufficient to determine positively the infection. This applies especially to the strictly intermittent fevers of tertian, quartan, or biquartan type, since there is no other disease that produces similarly recurring paroxysms for any length of time. Yet when we come to quotidian fever, difficulties begin to appear. Although it is the rule for malarial paroxysms to occur between midnight and midday, while other daily recurring fevers (for instance, hectic fever) choose the evening hours, this rule has so many exceptions that it would be dangerous to make a diagnosis from it. Septicopyemic fevers, like malarial paroxysms, frequently occur in the forenoon hours, and in phthisis a "typus inversus" is not infrequently seen. Still less do the continued or subcontinued fevers lend themselves to a diagnosis; on the contrary, it is exactly these which produce the greatest confusion. In regard to the paroxysm, we must remember that the three stages are usually developed in infections with parasites of the first group, and that the chill often fails in infections with the second group.

It is worth while insisting again that the thermometer is the only means of recognizing the existence of fever, and especially of diagnosing the type. The assertions of patients are entirely worthless, since subjective sensations are inaccurate. To determine the type it is necessary to allow several days to pass without specific modification, in the mean time taking the temperature regularly. Naturally this is to be done only when thereby no injury results to the patient.

Besides the typically recurring fever, there are typical repetitions of other symptoms, as pain, paralysis, abnormalities in secretion, etc., that may assist in the diagnosis of latent malaria; still it must be remembered that such repetitions occur apart from malaria, and that neuralgias especially intermit from other causes. In such a case it is well to bear in mind that latent fevers usually occur in individuals who have suffered before from malaria.

The *splenic tumor* is an important diagnostic characteristic. It is very rarely entirely wanting. Its presence confirms the diagnosis, yet it is not pathognomonic, since splenic tumors occur in most other infectious diseases, for instance, typhoid fever, miliary tuberculosis, and sepsis.

The large hard chronic splenic tumor may be produced by even more conditions, so that it signifies but little in malarial cachexia. In my experience splenic pain is of very subordinate value in diagnosis.

Skin Eruptions.—Herpes is significant, inasmuch as it occurs frequently in malaria, and but rarely in other conditions that might come into consideration, as typhoid fever, tuberculous meningitis, and miliary tuberculosis. Still, it is not peculiar to malaria, since it is seen in many other infections, as the ephemera, acute gastritis, rheumatism, colds, influenza, etc.

Urticaria is still less characteristic. Roseola is quite negatively diagnostic. Only very isolated cases of malaria with roseola have been reported. Other symptoms are much less characteristic of malaria, so that we will refrain from repeating them.

In concrete cases, other data, like the anamnesis and the "genius epidemicus loci," must be taken into consideration. In pernicious cases the fact that the patient has repeatedly suffered from malaria is of value, though it by no means absolves the physician from excluding other diseases in every intelligent way.

In places where malaria is endemic it is always before the eyes of the physician, especially in summer and autumn, while in regions free from the disease it is the last thing thought of, except when dealing with a patient who has come from a malarial district.

There is, therefore, in malarial regions, a decided tendency to pronounce every kind of an infection that is at all indefinite malaria, and this gives rise to many errors. With his mind constantly on the proteiform specter lurking *hic et ubique*, the physician readily follows it, since it facilitates diagnostic difficulties and gives him a ready diagnosis applicable to the worst cases.

Though we readily agree with Baccelli that the eye of the clinician should always be able to recognize malaria, even in its most grotesque garb, we must confess that only a very small number of physicians have the good fortune to possess a "clinical eye" that can be relied upon. For the majority, therefore, Laveran's discovery acts as an inestimable talisman.

Under certain circumstances the diagnosis *ex juvantibus* is of value. If a fever persistent for a long time is rapidly cured by quinin, there is a certain amount of probability that it was malaria. If the fever was strictly intermittent in type, the probability becomes almost certainty. Still, it would be extremely silly to pronounce every case malaria, whether or not it showed a temperature, simply because improvement or recovery followed quinin. Is it possible to designate it otherwise when a surgeon diagnoses as malaria a hemorrhage from the stump occurring several days after an operation for carcinoma of the tongue, and ceasing after the exhibition of quinin, simply because the individual suffered years before from malaria and the hemorrhage did not recur after a couple of grams of quinin?

The literature swarms with similar examples. Still, in contrast to this, the principle may be enunciated that there is no malaria when no temporary or absolute effect is produced on the temperature after several days' administration of quinin in proper doses. Laveran affirms that a continuation of the fever after the fourth day, in spite of the daily exhibition of 1.5 to 2.0 quinin, almost absolutely excludes malaria.

Yet in very severe infections the length of time must be increased. Ségard reports from Madagascar that the cases there usually begin as remittent or continued, and take on a tertian type only after six or seven days, and he asserts that quinin exercises but little influence during the primary stage. This simple and important rule is frequently forgotten, and it would not be at all difficult to give many instructive examples from my own experience.

A man living in a fever region suffered for seven months from intermittent paroxysms. He complained of pain in the left thorax, and manifested objectively an area of dulness below and posteriorly, over which bronchial breathing was audible. Chronic malarial pneumonia was diagnosticated, and the unfortunate man treated for months with quinin. In spite of the fact that the drug had not the slightest influence, the interesting diagnosis was adhered to. Finally a physician was found who doubted its correctness and made a puncture which showed thick pus. By thoracentesis there were evacuated about 1.5 liters of *pus bonum et laudabile.*

A woman suffered for a year from intermittent fever. Though no change was produced by weeks and months of quinin, and though the patient lived in a salubrious region, the diagnosis of malaria was not relinquished. An examination showed, in addition to the splenic tumor, swollen lymph-glands. At the end of the second year the exitus occurred in consequence of lymphosarcoma.

A woman from a malarial region suffered from violent, more or less regular, intermittent paroxysms of fever, mild jaundice, and enlargement of the liver and spleen. Quinin administered for weeks had no influence. In the blood no parasites were found. The anamnesis eventually aroused a suspicion of lues. Potassium iodid produced rapid recovery.

A gentleman from a malarial region suffered almost daily from recurring paroxysms of fever. He had become very pale and emaciated. Wherever he went he was treated with quinin, though without result. In a university town a consulting physician unfortunately discovered pigment in the blood, and the wretched man was fed again with quinin. A renewed examination of the blood by another consulting physician showed every sign of malaria wanting; but a foul-smelling discharge from the anus attracting his attention, the question was cleared up by a diagnosis of rectal carcinoma. This case teaches also that the blood examination must be carefully done.

From these few illustrations, which might easily be repeated ten times over, it is evident how little regard is bestowed on the rule that a fever which resists quinin for a long time is not malaria. The only absolute diagnostic characteristic of malaria is the occurrence of malarial parasites in the blood.

The results of expert investigators teach that the parasites may be found in almost every case. In Osler's clinic in Baltimore they were never wanting in 531 cases. The demonstration of the parasite, therefore, is not only of theoretic interest, but of considerable practical value. It possesses at least as much significance in malaria as Koch's bacillus in tuberculosis. The examination of the blood has accordingly become indispensable, and it is to be earnestly desired that the method obtain the widest prevalence not only among physicians practising in malarial regions, but everywhere. Malaria is carried by the infected individual, and under our present conditions of travel it is not difficult for people in Berlin or elsewhere to manifest attacks of pernicious fever acquired in Africa. Moreover, it is a well-known fact that physicians practising in regions free from malaria are helpless in regard to intermittent fevers, the causes of which are not evident, and that they too willingly jump at the diagnosis of malaria when a blood examination would solve the question.

The examination of the blood for the purpose of diagnosis may be done at any time during the day or night. Parasites are usually most numerous in the peripheral blood shortly before and at the beginning of the paroxysm. When possible, therefore, this time should be chosen.

If quinin has already been repeatedly administered in large doses, the chances of finding the parasites are much less, since under its influence the ordinary forms succumb and entirely disappear. Laveran's crescents alone constitute an exception. These appear to be absolutely insusceptible to quinin.

If the paroxysms have ceased for several days, either spontaneously or due to medication, the result of the examination is usually negative. This is especially true in cases of infection with parasites of the first group. In cases of parasites of the second group crescents may still be encountered long after the cessation of the fever.

The evidence of pigment is almost the same as that of the parasites themselves. It is only necessary to be sure that the pigment is actually malarial pigment. Black blocks and granules occurring free in the plasma are entirely valueless and without significance. They are foreign particles which contaminate the specimen in spite of the utmost care in preparation. Characteristic only is the reddish-black pigment inclosed in leukocytes seen in fresh preparations.

These melaniferous leukocytes are seen during the acute infection, and frequently one or two days after its commencement. Only in cases of infection with parasites of the second group do we find them, like the crescents, a long time after the attack. The rough granules of certain leukocytes which look dark in certain lights must not be confused with pigment. Lawrie's obstinate campaign against the malarial parasites was due to such an error.

It is well for the tyro to study normal blood thoroughly and for a long time under the strongest powers, so that in his search after malarial parasites he will not be confused by every ameboid leukocyte, swarming granule, vacuolated red blood-corpuscle, or blood-platelet. The beginner had better draw his conclusions only from typical parasites, and leave the pigment to more experienced eyes. Patience will always be rewarded. A single positive malarial parasite is absolute proof of infection.

Negative findings have only relative value, depending on whether the examination was done with sufficient expert knowledge and corresponding diligence. Even when this is true, a negative finding never means as much as a positive. Several preparations should, therefore, be examined at different times. If the examination is continually negative, a puncture of the spleen may be done in very important cases.

In my practice I have never been obliged to make a splenic puncture for the purpose of diagnosis. After repeated careful examinations I believe the exclusion of malaria is justifiable from negative findings.

It is usually only at the beginning of the infection that the parasites are so scanty as to occasion any considerable expense of time and labor. As a rule, they are found in the first preparation. If a microscope is at hand, it is advisable to examine the unstained blood at once; otherwise dried preparations must be made. In regard to the details of the examination and the sources of error, sufficient has been said in the section on Etiology.

If the malarial infection is proved, the next step in the microscopic examination is to determine the kind of parasite and whether the infection is light or severe. This has been described on page 91. A positive conclusion in regard to these details is possible in the great majority of cases.

I have often had the opportunity of proving the criteria which we owe especially to Golgi, Marchiafava, and Celli, and I can state that they have scarcely ever left me in the lurch. Only a short time ago I had a man before my class whose assertions in regard to his paroxysms were very confusing. The examination of the blood showed a double quartan, and to the astonishment of my hearers the paroxysms took place promptly as prognosticated. The differential diagnosis between malaria and its sequelæ, as well as between it and other acute and chronic diseases, is not infrequently necessary.

Among the fevers coming into consideration are: typhoid fever, sepsis in all its forms (for instance, sepsis in its narrow sense, septic fever from malignant neoplasms, from acute ulcerative endocarditis, from inflammation of the urogenital system, pyelitis, pyelonephritis, angiocholitis, hectic fever of phthisis), all kinds of pyemia, acute gastrointestinal catarrh, yellow fever, Malta fever, relapsing fever, miliary tuberculosis, and filaria disease, as well as other feverish conditions, like the fever of severe anemia, leukemia, malignant lymphoma, and hysteria.

If we add to these the different local syndromes of pernicious and latent fevers, still other diseases arise, requiring a differential diagnosis. We will refrain here from discussing all that might come into consideration, since the most important have been reviewed in the clinical part. Moreover, an examination of the blood is of more service and will lead to a more rapid diagnosis than the most acute reasoning.

The only absolute differential diagnostic characteristic between malaria and other infections is the malarial parasite, and every case not clear is to be diagnosed accordingly.

PROGNOSIS.

The prognosis of malaria is so different according to the kind of infection, the climatic conditions, and individual circumstances that little in general can be said about it. Certain rules valuable in general pathology may be laid down here.

The robust and young, not broken down by alcohol, with healthy organs, when well nursed and properly treated, have naturally a better prospect even in the severe forms of malaria than feeble, old cachectics whose resisting power has been diminished by alcohol, overwork, or deprivation, and who fail to obtain proper nursing.

In addition we can state that infections with parasites of the first group give *quoad vitam* an almost absolutely favorable prognosis,* while infection with parasites of the second group may terminate unfavorably. The blood examination, therefore, gives important information in the prognosis.

In infections with parasites of the second group the prognosis is further influenced by the clinical symptoms, as well as the individual characteristics of the patient and of the "genius epidemicus."

We have already called attention to the usual mortality when discussing the more important pernicious forms. According to L. Colin, the fatality of the pernicious fevers in an ascending scale is: Icteric, comatose, delirious, cardialgic, algid, syncopal.

When giving a prognosis in pernicious cases, we must remember that one attack may be followed after a longer or shorter interval by a second, third, etc.

This tendency to relapse and the danger of cachexia after repeated infections naturally aggravate the prognosis, thus making the fevers of the second group much more unfavorable.

Fevers of the second group usually relapse in spite of quinin; fevers of the first group, rarely. Some authorities ascribe to quartan fever an obstinacy in this direction, though others, with whom I agree, deny this. Nevertheless it appears that the tendency of quartan to spontaneous recovery is very slight, and its bad reputation probably comes from the time before the introduction of quinin. Moreover, though a positive and absolute cure usually follows the administration of quinin in cases of fevers of the first group, there are exceptions in which relapses occur in spite of the therapy.

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* Even Celsus writes (Lib. iii, Cap. xv): "Nam quartana neminem jugulat; sed si ex facta quotidiana est, in malis æger est; quod tamen, nisi culpa vel ægri vel curantis, nunquam fit."

We intend to introduce here a few figures from a large and mixed material which may serve to show the seriousness of malaria.

Beginning with *Italy*, since it is the most intensely infected civilized country, we find that in the years 1890, 1891, and 1892 there were 49,407 deaths from malaria, or 54 deaths annually among 100,000 inhabitants. In Rome alone there occurred—

In the year 1881	650 deaths.
" " 1882	505 "
" " 1892	139 "

In the severely infected parts of Italy 8 per cent. of the inhabitants yearly fall victims to it. In the year 1895 the Italian army had 4856 malarial cases in hospitals, of which 13 died.

Russia.—The Russian army showed, in 1881, 799,814 malarial cases, or 87.58 per cent. of the whole morbidity. Among these there were 279 deaths, or 0.35 per cent.

In the quinquennium from 1880 to 1884 the Russian army had an average morbidity of 75.83 per cent. from malaria (estimated from the whole force), with a mortality of 0.23 per cent.

Greece.—According to Pampoukis, 14,000 malarial cases, among 40,000 admissions, were admitted to the hospitals in Athens in the course of five years. According to the same writer, one-third of the morbidity throughout Greece was attributable to malaria. The mortality amounted to 4 : 10,000. Seven per cent. of the cases were pernicious and showed a mortality of from 21 to 33 per cent.

The mortality of the different forms was as follows:

General mortality	0.04 per cent.
Mortality from continued fever	0.70 " "
Mortality from pernicious fever	21.40 " "
Mortality from hemoglobinuria	6.60 " "

France and Algeria.—According to the latest reports, the French garrison in Algeria showed 100 to 200 cases of malaria per thousand of the force: the mortality did not exceed 1 to 2 per cent. How much the severity of the disease has diminished in Algeria is evident from the fact that in the year 1833 the garrison of Bona had, among 5500 men, 4097 malarial cases requiring hospital treatment, 830 of which died.

That there are even yet severe malarial foci in Algeria is shown by Verdan's report from the station Wargla. Among the natives there was a general morbidity of 648, with a mortality of 122, of which 167 and 110 respectively represent the figures for malaria.

In the Department Ille-et-Vilaine there occurred in 1873, among 10,089 inhabitants, 1696 cases of malaria, with 50 deaths.

In the Commune Bain alone, with 4266 inhabitants, there occurred, according to Dr. Blanche, 1866 cases (303 men, 596 women, 967 children); the above-mentioned 50 deaths occurred entirely in this small commune. Among the 50 deaths, there were 25 children (Woillez).*

In the year 1878 the Department Morbihan had 452 cases, with 195 deaths (Hérard); in 1880, 5705 cases, with 253 deaths; 1881, 2795 cases, with 191 deaths (L. Colin).

British India.—The English army in India, with a standing force of 64,137 men, showed, in the year 1892, a morbidity from "fevers" of 35,942 cases, with 474 deaths. Of these, 34,433 were malaria, with 98 deaths. The other deaths were due to "enteric fever," the majority of which were typhoid.

The native army, numbering 127,355 men, showed 66,989 cases of intermittent, with 125 deaths and 1676 remittent, with 181 deaths (Fayrer).

In Bengal 53,753 Europeans suffered from malaria. Among these there were 51,287 cases of quotidian type, with 646 deaths; 2097 of tertian type, with 12 deaths; and 369 of quartan type, with 2 deaths (Waring, quoted by Fayrer).

Madagascar.—During the French campaign in 1895 malaria raged frightfully among the French as well as the native troops. In the French Army of Occupation the deaths reached in a few months the enormous figure of 6000 (almost one-fourth of the entire force), so that Queen Ranavalo, of Tamatave, had reason to say: "The fever is my best general."

Ségard observed in Madagascar 15 deaths among 24 pernicious cases.

According to Quétaud, among a crew of 76 men on the ship "Thisbe" in Gabun (West Africa), 52 were attacked with malaria and 22 died.

Borius found in Sénégal that one-third of the pernicious cases ended fatally. Still, in certain places and at certain times milder forms occur, as is shown by the report of Cartier from Diego-Suarez in the year 1888. Among 1024 cases of malaria he had 4 deaths.

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* We must add that the civil sanitary records give the data of the deaths, though not of the number of cases, reports of which are not compulsory. The latter are, therefore, approximate.

We will not add to these statistics, since it is already clear how different the mortality may be under different circumstances. Rapid intelligent treatment under otherwise favorable conditions will give the best results.

SPONTANEOUS CURE.

It is an old, well-known fact that malaria frequently recovers even when quinin is not employed—in other words, in response to expectant treatment. These spontaneous cures have been observed, especially in hospital patients. Osler, in Johns Hopkins Hospital, left 58 cases to themselves and saw all of them recover spontaneously.

Spontaneous recovery takes place in infections with parasites of the second, as well as of the first, group; even pernicious cases may, under circumstances, cure spontaneously. Several such cases have been reported by Torti. The following are examples of spontaneous cure:

J. L., aged nineteen, says he has had a paroxysm daily for fourteen days; never had fever before. He is a robust youth, quite pale, subicteric in color. The spleen is evidently palpable. He complains of splenic pain and overfatigued limbs.

October 6, 1892: 10 A. M.: Temperature, 36.5°.

Blood examination: (1) Large pigmented parasites, almost the size of the blood-corpuscles, showing actively swarming pigment; (2) pretty numerous, likewise markedly pigmented parasites, filling half of the corpuscle. The infected blood-corpuscles are frequently swollen and decolorized.

Diagnosis: Double tertian.

3 P. M.: Temperature, 37°.

6 P. M.: Temperature, 37.5°. The expected paroxysm failed to occur. During the night, no sweating.

October 7: 10 A. M.: Temperature, 36.2°.

Blood examination: The same as yesterday afternoon, with, in addition, numerous melaniferous leukocytes.

4 P. M.: Temperature, 37.5°.

Blood examination: A very few large parasites.

6 P. M.: Temperature, 38°.

October 8: 10 A. M.: Temperature, 36.3°.

Blood examination: After a long search a large free parasite was found with actively swarming pigment. The patient manifested no further paroxysm, and nothing further was found in the blood.

P., aged forty-seven, asserts that he has had violent typical paroxysms daily for four days.

September 21: 3.30 P. M.: Temperature, 40.3°; pulse, 120; tension subnormal. Slight icterus; the spleen extends beyond the border of the ribs about two fingerbreadths.

Blood examination: A few non-pigmented ameboid parasites.

September 22: During the night, a profuse sweat.

9 A. M.: Temperature, 35.8°.

Blood examination: Isolated, small, immovable parasites in ring form; no pigment.

4.30 P. M.: Chill; temperature, 39°.

5.30 P. M.: Temperature, 40°; chill still continues.

8 P. M.: Temperature, 40.2°.

September 23: 9 A. M.: Temperature, 36.7°. Patient very much exhausted; the spleen has greatly increased in size since yesterday.

Blood examination: A very few small parasites, immovable, in ring form.

6 P. M.: Apyretic.

September 24: Apyretic.

Blood examination: Two melaniferous leukocytes; no parasites.

September 28: The patient has remained apyretic.

Blood examination: Crescents.

In both these cases the treatment was expectant. As is evident, the first was a case of infection with the common tertian parasite; the second, with the genuine quotidian parasite.

The problem as to how the organism gets rid of the parasites may be regarded as partially solved. It is likely that the quiet, the nursing, and the malaria-free air of the hospital strengthen the organism in its struggle against the parasites, at least against new infections; though the significance of this is not great on account of the eight to fourteen days' incubation of malaria.

Further, Metschnikoff has shown that the macrophages of the spleen and bone-marrow develop an energetic phagocytic activity. Bignami, as we have seen in the section on Pathologic Anatomy, devoted special attention to this. He found that the macrophages of the spleen and of the bone-marrow took up large numbers of parasites in every stage of development. The endothelium of the splenic, hepatic, and cerebral vessels, likewise, manifest this phagocytic power, though in a slighter degree. Still, occasionally the endothelial cells seem to participate more actively—for instance, Barker reports a case in which the endothelium of the liver capillaries and Kupffer's cells were packed with parasites.

In addition to the macrophages, the vascular endothelium, and Kupffer's cells, the circulating leukocytes play a rôle in phagocytosis. True, we never find leukocytes inclosing recognizable parasites either in freshly made natural preparations or in dry stained ones; yet after observing a natural preparation protected from evaporation for some time it is not rare to see a polynuclear leukocyte gradually approach a parasite, even one with flagella, and take it up. The movement of the pigment in the parasite continues for a short time in the body of the leukocyte and then ceases. The contour of the parasite gradually disappears until nothing but the pigment remains as a recognizable remnant. It is much more rare to see the parasites taken up by lymphocytes, and the greatest rarity by eosinophiles.

It has not been absolutely determined that the leukocytes possess this phagocytic power in the circulating blood, and the fact that in fresh preparations there is no suggestion of it seems to speak against it. We do not know even how much of the phagocytic action on the part of the macrophages and endothelial cells is postmortem and how much *intra vitam*.

Moreover, it is worth recalling that the number of leukocytes is usually decreased in malaria. Billings (quoted by Barker), as well as Bastianelli, found that during a paroxysm there was a decrease in the polynuclear and an increase in the large mononuclear cells, while the small mononuclear and eosinophile cells showed no regular deviations from the normal.

Vincent found similar results; namely, immediately after the beginning of the paroxysm a very transitory, more or less considerable leukocytosis, due especially to lymphocytes, less so to eosinophile and large mononuclear cells, while the polynuclear cells did not participate at all. This leukocytosis disappeared within a few minutes, and on the development of the hot stage a leukopenia took place. This alteration in the number of leukocytes is by no means characteristic of the malarial paroxysm, since it has also been observed in other infections.

Kelsch, who first called attention to the decrease in leukocytes (1: 2000 in comparison with the erythrocytes) during the acute infection, found that on strong faradization of the spleen the number of leukocytes in the peripheral blood increased. From this he concluded that the leukocytes had accumulated in the spleen and were forced into the circulation by the contraction of the organ. He found an increase in leukocytes only in pernicious cases (1:48).

Whether there is a causal connection between the leukocytosis and the perniciousness is uncertain. I have suggested the possibility that under normal conditions the polynuclear leukocytes collect in the spleen, where, favored by the slowing of the blood-current, they are able to consume the parasites and thereby decrease the infection; under other conditions they remain in the circulation, where they cannot exercise this activity, and the infection, as a consequence, becomes severer.

Golgi affirms a rhythm in the phagocytic activity of the leukocytes which runs parallel to the fever. In quartan and tertian fever, for instance, this phagocytosis begins with the paroxysm and continues three or four hours afterward.

This fact I can confirm, namely, that the greatest number of melaniferous leukocytes is found at the time of the paroxysm and shortly after it. Yet this is not so on account of any "cyclic function" on the part of the leukocytes, but because the segmentation of the parasites at this time sets the pigment free, and it falls to the duty of the leukocytes to carry it away. Possibly, too, chemotaxis comes into play. I regard the melaniferous leukocytes not as parasite-eating phagocytes, but rather phagocytes whose duty it is to remove only the lifeless pigment.

All in all, from the investigations of Metschnikoff, Guarnieri, Bignami, Marchiafava, and others, it would appear that phagocytosis was principally an affair of the macrophages and endothelial cells; though the usefulness of the macrophages would be to a certain extent impaired, if, according to Bignami, many of them degenerate before they have digested the parasites they have taken up. The rôle of the circulating leukocytes appears to limit itself to the removal of the pigment, the cadavers of parasites, etc.

In addition to phagocytosis, other factors come into consideration in the spontaneous cure. We have stated in another section that by no means all the parasites reach the stage of segmentation, but that a considerable number are interrupted in their development, when they break up and die. We may recall the dropsical, distended, sterile forms of the tertian parasite, and it is to be assumed that the same thing occurs in other species.

Further, during the fever paroxysm many fragments of parasites are observed circulating in the blood. These are the remains of large parasites which have been broken up by the specific action of the blood-serum, of the parasitic toxin itself, or other unknown causes.

From the standpoint of our present knowledge, therefore, we may say that spontaneous cure is the result of phagocytosis, of the sterility of numerous adult forms, and of the destruction of free parasites during the fever paroxysm.

The question now arises, Is it proper to wait for spontaneous cure and leave the patient to his fate? To this there is only one answer, namely, quinin must be administered in every case of malaria, even if spontaneous cure has already set in, unless it is excluded by very definite contraindications.

We must at the present time allow that a number of parasites may exist in the blood or in the internal organs, and even increase there, without, at least for a certain period, producing symptoms. I have seen such cases repeatedly, and Vincenzi has published interesting observations about others. This condition is usually seen in old malarial patients. The apyrexia, therefore, cannot be trusted, and for the sake of certainty quinin should be administered in order to prevent increase of the anemia and subsequent relapses. In cases of a severe character it would be decidedly injudicious to wait for spontaneous cure.

TREATMENT.

Malaria is one of the few infectious diseases for which we possess a positive specific. What an inestimable blessing quinin has been to humanity can be realized only by reading the writings of former times, when physicians were powerless against malaria and wore themselves and their patients out with useless and fantastic endeavors, and comparing them with Morton's or Torti's jubilations over their success with the wonderful drug.

Let us turn back a little and examine how malaria was treated in the ancient times. The therapy of the Greeks consisted principally in dietetic regulations. What should be eaten and drunk at every hour of the day was accurately determined for every kind of fever. They recommended also the drinking of large quantities of wine, baths, and inunctions.

Cleophantus* in tertian fever advised wine internally and the pouring of hot water on the head for a long time before the paroxysm. Asclepias repudiated these doubtful curative measures.

According to Celsus, the therapy of Rome followed that of Greece. Before the outbreak of the chill patients were put in a warm bath. If this did not suffice, onions or warm water with pepper were administered, or warm poultices, warm potsherd, or inunctions with warm oil were employed. The regulation of diet was also important. In especially obstinate cases the patients were put on board vessels and sent to sea. They appear to have attributed the result of sea-voyages not to the change of place, but to the movement; consequently patients were carried about in the streets or even in their dwelling. These simple regulations, at least, did not injure the patient.

The physicians of the middle ages, not content with this treatment, set up in its place a conglomeration of measures which recall more the Inquisition than medical treatment. It makes one shudder to read, for instance, the method by which Ludovicus Mercatus, otherwise so gifted, treated pernicious fever. He began with purges of manna, cassia fistula, and infus. rhei, followed by venesection of the right basilic vein, frictions, fumigations, constriction of the extremities, cuppings, etc.

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* Quoted by Celsus, Cap. xiii.

Torti, who had the good fortune to be one of the first to employ Peruvian bark to any extent against malaria, writes in relation to the pernicious cases which he was previously forced to treat without it: "Nonnullas equidem, antequam in iisdem curandis Cortice uterer, etiam sine illo sanatas vidi; at paucas et difficillime."[*]

In 1639, with the introduction of cinchona bark, a new age opened for malarial patients. The following is the memorable history of this great discovery, according to Markham (translated by Binz):

"In 1638 the Countess of Cinchon, the wife of the Viceroy of Peru, lay very ill with tertian fever at Lima, the capital city. The news was carried to Canizares, then Corregidor of Loxa, a town among the Andes in the present Ecuador. Though the natives in Peru were unacquainted with the curative power of the bark, those of the more northern lying countries appreciated its worth, and from them Canizares obtained the secret. He therefore sent a parcel of it to the vice-queen. Her physician, de Vega, agreed to its employment and she recovered in a short time. In 1640 the Countess returned to Spain and carried with her a large quantity of the precious bark, which she distributed about her native place in the vicinity of Madrid. De Vega followed and brought likewise a large amount of the bark to Spain, which he sold at Seville for a hundred reales a pound. The Countess employed the bark so extensively that for a long time it bore the name 'Countess's powder' (pulvis comitissæ), and Markham asserts that even to-day the fame of her deeds in that region of Spain continues. The Jesuits, who were the missionaries to South America, also did good service in introducing the bark and spreading a knowledge of it.[†]

"In the year 1642 the first paper appeared on it,[‡] and though in the beginning frequently condemned as useless, fraudulent, and injurious, the bark was admitted to be indispensable before the end and the greatest part of it now comes from these countries. The following data in this regard are from Moëns. In the year 1880 there was exported from—

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[*] Note to Mercatus, Scholium iv, Lib. ii, Cap. ii.

[†] Morton writes in relation to this: "Circa annum salutis 1649 famam suam (sc. Corticis) in dies magis, magisque provexit, non tantum per Hispaniam verum etiam Italian, Roman usque, conatibus imprimis Johannis Cardinalis de Lugo Soc. Jesu, et cæterorum Collegii Jesuitarum Romas Patrum, qui eum gratis religiosis et pauperibus largiebantur. Unde infausto omine, atque in vulgi reformati terrorem, ac scandalum Pulvis Patrum vulgo audit (anglice, The Jesuit's Powder). Quo nomine plurimos, illosque non sortis gregariæ, in hunc usque diem, ab ejus usu abhorrere contigit, ac si, nam naturalium remedium fuisset, sed factitium, diabolicum et venenatum arte Jesuitarum paratum, potius quam divinæ φιλανθρωπῖας donum."

[‡] P. Barba, "Vera praxis ad curationem Tertianæ," Seville, 1642.

Java	123,941	kilos bark
English India	208,056	" "
Ceylon	526,381	" "

The same writer has published an excellent work on the cultivation of cinchona in Asia, and he describes as the most useful species: *Cinchona succirubra*, Pav.; the different *C. Calisaya* Wedd.; *C. officinalis* L.; and the *C. lancifolia* Mutis. The bark should contain at least 5 per cent. of quinin and its allied alkaloids.

The chief constituents of Peruvian bark are: *Quinin* ($C_{20}H_{24}N_2O_2$). This is a biacid base. Its anhydrid is a white, amorphous substance of very bitter taste. It is but only slightly soluble in water (1 part in 400 of cold or 250 of boiling water). It forms crystallizable salts which are readily soluble in water, and which are, therefore, employed in therapy.

Cinchonin ($C_{19}H_{22}N_2O$).
$\left.\begin{array}{l}\text{Chinidin}\\ \text{Chinicin}\end{array}\right\}$ isomeric with quinin.
$\left.\begin{array}{l}\text{Cinchonidin}\\ \text{Cinchonicin}\end{array}\right\}$ isomeric with cinchonin.
Chinovin ($C_{30}H_{48}O_8$), a bitter-tasting glucosid.
Cinchonic acid ($C_7H_{12}O_6$), associated in the bark principally with quinin.
Cinchotannic acid.

Chinoidin is an amorphous decomposition-product obtained in the preparation of quinin. Its constitution is very variable.

Of all these, quinin and its salts possess the greatest therapeutic value. They are, therefore, the most commonly employed, both in a curative and prophylactic way.

The manner in which quinin acts in malaria has been set forth by us as follows*:

"The effect of quinin on the malarial parasites has been studied both by Laveran himself and other investigators. Laveran made his investigations in this way: He prepared two blood specimens simultaneously from a patient. He examined one as it was, the other after treatment with a very dilute solution of quinin. He found that the parasites in the control preparation continued actively motile for some time, while in the quinin preparation they lay still and lifeless. From this the direct poisonous action of the drug on the parasites seemed evident.

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* *Loc. cit.*, p. 170.

"If the quinin has been exhibited in two or three doses of 0.5, four to six hours before the paroxysm, tertian parasites may sporulate normally or may be checked before reaching full development. We will return to these later when speaking of the structure of quinin forms.

"In the medium-sized quartan parasites Golgi observed a less fine granulation, a metallic luster, and an inclination to shrinking. The large forms were swollen, showed lively oscillatory movement of the pigment, and sometimes contained vacuoles or abortive spores.

"As is evident, these two species, closely related normally, show too a marked similarity in their behavior toward quinin. The small, crescent-forming parasites can be studied better in stained than in unstained preparations.

"Baccelli observed that the ameboid organisms showed at first an increased liveliness of movement, but after twenty-four hours the majority had usually disappeared.

"In cases of quotidian of a mild character, I have found, three hours after a dose of 0.5 quinin, that the nucleoli of some of the ameboid organisms either did not stain or stained very poorly. On continuing the therapy for a further twelve hours I found only isolated parasites with a nucleolus, and many of the remainder were in process of breaking up; some, in fact, showing only a few amorphous fragments.

"The failure of the nuclear chromatin to take the stain indicates naturally beginning necrosis. This is quickly followed by complete destruction, and, after forty-eight hours, nothing more can be seen of the parasite.

"The action of quinin on the tertian parasites is very similar. I found that a few hours after the first administration of quinin the majority of the small and medium-sized forms no longer showed stainable nucleoli, while the clear vesicle, representing the nucleus, was seen as before. The further fate of these necrotic parasites consisted likewise in destruction.

"I found, further, that some sporulation forms manifested peculiar changes when the quinin had been administered several hours before the paroxysm; namely, a segmentation, which appeared complete in unstained preparations, but which, when stained, showed spores capable of life—that is, with well-developed structure—in only a small portion of the segment, while the remaining showed no nucleoli and were, therefore, incapable of life.

"From this I concluded that, under the action of quinin, segmentation may be abortive, and I, therefore, named these segments without nuclei dead-born spores.

"Yet it is possible that Golgi's opinion, after a like observation, is the correct one, namely, that the spores died only after they had been formed capable of life. Between these two possibilities there is no important difference.

"According to Romanowsky, the adult large parasites manifest a most decided effect in that they often show no nucleoli and only diffusely stained nuclei. I mentioned before that I consider the diffuse staining of the nucleus and the disappearance of the nucleolus in the large forms not necessarily as necrosis, but sometimes as a preparatory stage to sporulation. I believe, therefore, the young forms without nuclei are decidedly more characteristic for the action of quinin than those described by Romanowsky. In accordance with my observation, Roman-its action on the innervation of vessels, on the heart, on oxidation, on diapedesis, the white blood-corpuscles—are of secondary or of no importance. If the paralysis of the leukocytes by solutions of quinin, discovered by Binz, signifies anything in the therapy of malaria is doubtful. The frequent occurrence of melaniferous leukocytes after the paroxysms tends rather to the conclusion that the activity of the white cells is not interfered with.

PREPARATIONS OF QUININ. METHODS OF ADMINISTRATION.

The number of quinin salts manufactured and put on the market is very large. In the last edition of Ewald's "Handbuch der Arzneiverordnungslehre" (thirteenth edition, 1898) I counted, apart from quinin, not fewer than 33 quinin salts. That the great majority of these are superfluous scarcely needs mention.

The Austrian Pharmacopœia of the year 1889 gave the following preparations as official: Quinin bisulphate, ferrocitrate, hydrochlorate, sulphate, and tannate. The German Pharmacopœia considers official quinin ferrocitrate, hydrochlorate, sulphate, and tannate.

Among these preparations the hydrochlorate and bisulphate deserve the preference. Both are readily soluble (the first in 34, the second in 11, parts of water), and both contain relatively large amounts of the active principle. The first has this advantage over the second that its watery solutions are less inclined to become moldy.

The quinin may be introduced into the organism per os, per rectum, endermatically, subcutaneously, and intravenously.*

Each of these methods of administration, omitting the endermatic one, which was abandoned as useless, has its indication. The common method of administration is per os. It is to be preferred in mild cases of intermittent, remittent, or subcontinued fever as long as an uncontrollable vomiting does not render it futile, and as long as pernicious symptoms do not demand the more rapidly acting subcutaneous injection. Quinin is administered per os in solution, powders, pills, and tablets. The solution has the undoubted advantage of being more quickly absorbed, thereby producing a more marked effect. In armies it has been generally employed with good results. The patient should be compelled to swallow the solution in the presence of the physician, in order to prevent deception. As a corrigent, a piece of lemon-peel may be employed.

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* As a matter of curiosity, we may mention that even up to the beginning of this century Peruvian bark was employed as an addition to baths, as well as sometimes "sewed between two shirts" (Reil).

The repulsive bitter taste has succeeded, however, in spreading the employment in powder form in civil practice. Pills, pralines, and tablets are inadvisable, on account of their possible insolubility, though they must occasionally be employed in the case of sensitive people and children.

As tasty corrigents may be recommended syrup. liquiritiæ, coffee with cognac, different fruit-juices, and milk. For children between four and six years Créquy recommends:

℞.	Quinin. muriat.	0.30
	Syr. liquiritiæ	3.00
	Aquæ	40.00

Some persons experience a burning in the stomach after taking quinin. In such cases Liégeois recommends its administration with equal parts of antipyrin.

Per rectum* the drug is exhibited in lukewarm clysters to which several drops of the tincture of opium may be added to aid retention. A cleansing injection must be given previously.

The endermatic method, as mentioned previously, has been entirely abandoned. Only minimum quantities of the drug penetrate the intact skin, and its application to places where the epidermis has been removed by vesicants is both painful and uncertain.

The subcutaneous or intramuscular injection of quinin is, on the contrary, of special importance. It is indicated in all cases in which severe symptoms demand prompt interference. It is, therefore, employed considerably in malarial regions, and has proved itself of inestimable value in pernicious malaria.

The injections must naturally be made under special precautions,

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* According to Torti, Hadrianus Helvetius was the first to recommend the administration per rectum. Torti himself used this method in severe infections. We may prescribe, for instance:

℞.	Quinin. hydrochlor.	1.0
	Aquæ	200.0
	Tr. opii spl.	10 drops

Sig.—Two clysters.

℞.	Quinin. hydrochlor.	1.5
	Butyri cacao, q. s. ut ft. suppositoria No. 5.	

Sig.—Suppositories.

otherwise inflammation, abscess, or phlegmon may result. In warm countries even tetanus has been observed to follow the injections (Vincent and Burot). It is consequently necessary to disinfect the skin by washing it with soap and water, alcohol, and bichlorid of mercury. The syringe should be made entirely of glass, with a needle of platin-iridium. Before employment it should be boiled and the needle heated to a red heat. The injection may be made either subcutaneously or into the muscles, preferably those of the gluteal region. No matter what solution is used, the injection is always more or less painful.

The solution should be sterilized. If crystals precipitate, they should be dissolved by renewed warming. The most commonly employed salt is quinin bimuriate. It is best to have at hand sterilized solutions of this in a proportion of 1: 2 in glass vials, each serving for one injection.* In other cases the following solution may be prepared:

℞. Quinin. bimuriat.	5.0 grams.
Aquæ dest. et sterilisat.	10.0 c.c.

One injection of 1 c.c. contains 0.5 quinin.

According to Beurmann and Villejean, in the absence of quinin bimuriate it may be readily prepared from quinin muriate by adding to the latter an equal quantity by weight of hydrochloric acid (D = 1045),† and to the solution obtained, an equal quantity of water. This makes a solution which contains 0.5 quinin bimuriate in every 1 c.c.

Injections of quinin bihydrochlorate are almost painless. The same is also said of quinin bihydrobromate. Solutions of this latter 1 to 3 to 10 of water are injected warm.

Von Stoffella dissolves, under light warming, 2.0 quinin muriate in 10 c.c. distilled water, and injects the solution lukewarm. He claims that the injection is painless.

La Bord and Grimmaux recommend:

℞. Quinin. hydrochlorico-sulph.	5.0 grams
Aquæ dest.	10.0 c.c.

M. D. S. injection.
1 c.c. = 0.5 of the drug.

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* These vials may be procured, among other places, in the Kade'schen Oranien-Apotheke in Berlin (Plehn).

† Official hydrochloric acid is diluted with distilled water until the aërometer shows a specific gravity of 1045. Then, for instance, 5 gm. quinin muriate is dissolved in as much of the acid as will eventually make 5 c.c.

In severer cases he gave at once 2 drams and says: "Neque enim sex scrupuli v. gr. pulveris, per sex successivos dies assumpti, æquivalent activitati, licet æquivaleant ponderi duarum drachmarum uno hausta assumptarum; quod, ut maxime verum est, ita et maxime notandum in praxi."*

SPECIAL TREATMENT.

Intermittent Fever.—To adults 0.3 to 0.5 quinin hydrochlorate or bihydrochlorate is administered three to five hours after the expected paroxysm. This is repeated four or five days, even when no further paroxysm occurs.

In order to prevent a relapse, a week after the last paroxysm a similar dose is administered two or three days in succession, at the same time of the day as previously. This is repeated a week later. After this, in cases of infection with parasites of the first group, we may reckon with considerable certainty on the non-occurrence of a relapse, naturally omitting new infection.

In the case of malignant tertian, the paroxysms of which are very long, the intermissions or remissions short, the blood examination must act as a basis for the therapy. The occurrence of a large number of parasites with concentrated pigment announces the approach of a paroxysm. The remedy, therefore, is to be administered at this time.

Continued or Remittent Fever.—After determining the diagnosis, 1.5 to 2.0 quinin is to be administered within two to four hours either per os, or, if vomiting results, hypodermically. Clysters are less efficacious. One gram should be repeated every twelve hours until a fall of temperature takes place, and later every twenty-four hours for four to six days.

It must be remembered that these fevers usually relapse obstinately, and that the blood examination is the only basis for a rational therapy. As long as crescents alone are visible quinin is useless, but as soon as ameboid organisms appear, 1.0 pro die should be pushed until they have vanished. This must be repeated while the blood examination shows the continuance of the infection. In these cases we actually have to do with a fractional sterilization of the blood.

When not in the position to control the case by microscopic examinations of the blood, quinin should be administered in a similar way to that described for intermittent fever and continued from week to week.

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* *Loc. cit.*, p. 56.

fests a severe malarial infection (numerous parasites on examination) and at the same time an assured intolerance to quinin in the shape of hemoglobinuria, the decision is very difficult.

In such cases we must bear in mind that the patient's life may be endangered by one dose of quinin and again by the omission of it, on account of increasing infection. Something must be done, and there is no time for experimentation with other remedies. Consequently if the symptoms continue to increase in severity, there is nothing to do but play *va banque* and grasp at quinin. Not too small a dose should be given, for then nothing is accomplished in regard to the infection, and a paroxysm of hemoglobinuria is produced just the same. Still, we cannot recommend Steudel's colossal doses of 8 to 10 gm. pro die, but would suggest 1.0 to 2.0.

Tomaselli went to considerable trouble to find a substitute for quinin for these cases, or at least a means by which its poisonous property would be rendered inactive, but without result. In one case only he succeeded in evading the paroxysm by the simultaneous employment of opium with the quinin. Coglitore asserts that he has obtained good results by a combination of quinin with opium and ergotin. He recommends:

℞. Quinin. sulph.	0.75
Ergotin. Bonjean	0.30
Opium	0.05

SIG.—Div. in dos. iii. One powder every hour.

Further observations are required to determine the value of this combination.*

Statistics as to the results of different methods of treatment of malarial hemoglobinuria are of only relative value, since among the differently treated cases there would be a large percentage of individuals with quinin intoxication.

Moreover, as mentioned by Corre, the results of treatment fluctuate within wide limits, according to time and place, even under exactly similar therapy; in other words, the matter is complicated by an unknown factor, the interference of which cannot be avoided. Nevertheless, we intend to introduce a few of these statistics, since better are wanting.

We take the following statistics from Bérenger-Féraud. To make them intelligible we must say that this physician believes in energetic treatment with quinin. He gives 3.5 to 4.0 quinin pro die, together with quite large doses of opium. The letters standing before the different rows indicate military medical men under whose assistance the treatment was carried out. The cases occurred in West Africa.

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* In one case Livio Vincenzi was unsuccessful with this combination.

	Number of Patients.	Deaths.	Percentage Mortality.	Treatment.
A	71	22	31	Quinin in very small doses. Calomel.
B	40	8	20	Quinin in moderate doses. Calomel in very small doses.
C	29	5	17	
D	11	4	36	Quinin in very small doses. Calomel and other purgatives as a basis of treatment.
E	42	13	31	
F	30	9	30	
G	45	5	13	Quinin in large doses.
H	18	0	0	
Total	286	66	23	

Tyson had, among 24 cases, 33.8 per cent. of recoveries with quinin, and 25 per cent. of recoveries without quinin; Webb, among 33 cases, 69.6 per cent. of recoveries with quinin, all deaths without quinin.

Steudel (East Africa), who recommends large doses and employs in the first days of the disease 8.0 quinin (once even 10.0 quinin), had among 18 cases 3 deaths, or 16 to 17 per cent.

In contrast to these favorable data the following seem to show the opposite for the treatment with quinin:

Daniel reckoned, among 93 cases, 82 per cent. of recoveries and 18 per cent. of deaths by treatment without quinin, and 59 per cent. of recoveries and 41 per cent. of deaths with quinin.

Albert Plehn (Kamerun) had, among 53 cases, 5 deaths, or 9.8 per cent. mortality, under moderate treatment with quinin. This last-named authority formulates the following principle for the treatment of blackwater fever*:

"1. Quinin is superfluous, because the enemy which it is to combat succumbs in a short time from its own activity.

"2. Quinin is in the highest degree dangerous, on account of its tendency to produce new paroxysms by renewed disorganization of the blood after the first have happily passed."

After reading the very interesting and instructive anamneses of Plehn, we cannot resist the impression that many of his cases of blackwater fever were nothing else than quinin intoxication. According to Plehn's own statement, among the 53 paroxysms observed by him, 48 were "produced" by quinin, or, at least, followed its administration.

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* *Loc. cit.*, p. 56.

We cannot agree, therefore, with his conclusions for the following reasons:

Almost all of his cases took quinin either on account of general indisposition or fever. Although after this (omitting the fact whether it was only *post hoc* or actually *propter hoc*) a paroxysm of hemoglobinuria occurred, the quinin exercised, nevertheless, its antiparasitic effect. For only in this way can be explained the very small number of parasites which Plehn found in the majority of the cases that he examined. After these patients had been restored to health it was impossible to say that they would have recovered without quinin, but only that the small doses which they took before the paroxysm had been sufficient. Plehn's view that the parasites succumb after they are liberated by the destruction of the corpuscles may be correct, but it is also true that the quinin could act more readily on these than on the intraglobular parasites, and so exercise, in smaller doses, a more marked effect than ordinarily.

Moreover, we understand, from Plehn's histories, that he permitted the paroxysm of hemoglobinuria to pass under purely symptomatic treatment, yet when fever occurred again which he found himself unable to master, he turned every time to quinin, and with advantage.

Altogether, it seems to be determined that a rational therapy requires strict attention to both infection and idiosyncrasy to quinin, as well as a thorough study of the individual case from these points of view. The treatment of blackwater fever is one of the most difficult and serious problems of the tropical physician. On account of the uncertainty surrounding these cases, especially when the examination of the blood is ignored, different methods of treatment arose.

Still, some of these manifest much that is good, since they are based on the symptomatic indications, which are of considerable importance. The patients suffer, for instance, excruciating torments, which naturally call for relief.

Therefore we do not hesitate to introduce several of these methods. Though we must refer at the same time to a subsequent section for the further symptomatic treatment of malaria.

Quennec obtained good results in 22 cases, with the following treatment: In addition to moderate doses of quinin, he administered 4 to 6 gm. chloroform pro die, in the following combination:

℞. Chloroform	4.0–6.0
Gummi arab., q. s.	
Sugar water	250.0

Of this, the patient takes a swallow every ten minutes. The vomiting and singultus are favorably influenced, and the diuresis relieved.

He recommends also saline purges, together with high cold injections into the intestine (sodium chlorid 10; water 1000). Hébrard obtained good results in two cases from the same treatment.

Rangé recommends the following therapy: At the beginning of the first paroxysm, six wet-cups to the lumbar region and an injection of quinin hydrobromate, with three drops of ergotin. Internally, infus. sennæ with manna and three glasses of boiled Kinkélibah (see below). He claims that after forty-eight to sixty hours the urine regularly becomes clear.

We cannot conceal that with the already severe destruction of the blood we consider blood-letting decidedly contraindicated.

Ségard observed good results from 1 or 2 gm. tannin pro die, administered internally during the paroxysm. He gave quinin only after the hemoglobinuria had passed. Cazes recommends no quinin, and instead, applications of moxa and Vienna caustic paste to the renal and hepatic regions.

Guillaud's "method of treatment" (1887) is offered to show that medical science has not yet passed its middle ages. In addition to giving large doses of ipecac and quinin—60 grams (!)—he applied blood-leeches and wet-cups to the renal region (he did this repeatedly on the same patient).

In the tropics calomel and ipecac are administered in superabundance in this as well as other forms of malaria; in our opinion, too routinely and without sufficient indication.

The transfusion of blood, recommended by Steudel, as well as the inhalations of oxygen practised by Baccelli, are worthy of the warmest commendation.

It is possible, too, that subcutaneous infusion of salt-solution would be of advantage. Plehn warns, and correctly, against the employment of alcohol during the paroxysm. Some writers express doubt as to whether, in cases of uncontrollable vomiting associated with tormenting thirst, the patient should be allowed to drink, since, as a rule, the drink is immediately vomited. It seems to us that rectal infusions or subcutaneous injections of salt-solution are most adapted to replace the loss of fluid in the tissues. The relieving of the thirst by iced drinks is no more than an act of humanity. Unfortunately, the necessary ice is not rarely wanting.

ADDITIONAL EFFECTS OF QUININ.

It is well known that quinin produces, in the majority of people, additional mild or severe effects. Many complain of a sensation of pressure in the stomach, which may even lead to vomiting. Still, this intolerance of the stomach is rarely so marked as to prevent administration per os (omitting, naturally, those cases in which vomiting is a symptom of the infection).

Very frequently, in fact, almost constantly, it produces a ringing in the ears, associated with a certain amount of deafness, and often vertigo of light degree.

Sometimes a toxic erythema occurs, which may even scale and be mistaken by the inexperienced for scarlet fever. Urticaria and purpura hæmorrhagica have been observed. Schulz noted in several healthy persons, after the administration of 0.5 to 1.0 quinin for neuralgia of the fifth nerve, diuresis and polyuria.

Again, there are persons who show a decided idiosyncrasy to even moderate doses of the drug. Schwabach reports the case of a man, thirty-seven years old, who, after 1.2 quinin muriate, was attacked by a violent tinnitus aurium, pain in the left ear, stupor, attacks of vertigo, and marked deafness. The hearing remained affected for months.

Trousseau and Pidoux mention a nun who was made insane for a day by 1.2 quinin, and another case that, after one dose of 3.0 quinin sulphate, suffered from ringing in the ears, attacks of vertigo, and uncontrollable vomiting, followed seven hours later by blindness, deafness, delirium, and inability to walk. Recovery was complete.

Floyer observed, in a man of forty, after 0.15 quinin, wide-spread urticaria over the body and intense dyspnea, associated with fear of imminent death.

Rizu saw a woman attacked with violent sneezing from 0.10 quinin taken on account of tertian. The face became turgid, the secretion of tears profuse, and an attack of orthopnea followed. The skin, bathed in a profuse sweat, broke out in urticaria. This condition repeated itself every time the woman took quinin.

Symptoms of poisoning after the large doses sometimes administered by physicians are not at all infrequent. Deafness and bilateral blindness are especially sources of worry and torment to the patient. Both conditions are usually transitory, though a contraction of the field of vision may persist.

Geschwind found, in a case of amblyopia following a continuous administration of quinin, a filaceous clouding of the vitreous humor, which might explain the persistence of the derangement of vision.

Under certain circumstances large doses produce extremely threatening symptoms. Roberts observed the following symptoms in a woman after 8.10 quinin sulphate: Unconsciousness, fall of temperature, general lividity, slowed superficial respiration, small, thready pulse (45 to the minute), pupils widely dilated, staring, abolishment of tendon and skin reflexes, coffee-ground vomit, in addition to deafness that lasted a week and blindness that continued five months.

Pispiris observed intestinal hemorrhage after quinin in two cases of malarial anemia.

Küchel, who gives in blackwater fever up to 8.0 pro die, observed once, out of four cases, amaurosis which persisted fourteen days.

Isolated cases of fatal poisoning have also been reported. The following observation of Baills is very interesting:

Two soldiers took by mistake 12.0 quinin sulphate in solution. Soon after they complained of intense ringing in the ears, total deafness, and cramps in the stomach. The skin became extremely pale, the pupils dilated, respiration became superficial, the skin cool, and the pulse slow, small, irregular, and at times impalpable. Auscultation of the heart showed scarcely audible, frequent jerky sounds, and both sounds were frequently run together. One died four hours later in syncope; the other recovered. The autopsy was negative. This case seems to indicate that in large doses quinin acts as a cardiac poison.

In some places metrorrhagia and abortion are attributed to it. Burdel reports five cases of pregnant women who gave birth to stillborn children after large doses of quinin on an empty stomach.

According to the unanimous experience of responsible observers, these effects cannot be laid at the door of quinin. Many obstetricians hold that quinin strengthens uterine contraction during labor, and they, therefore, recommend it in place of ergotin, though they deny that it is able to initiate the contractions and so produce a premature birth. The former belief, which is nothing more than a superstition of some malarial regions, is based on the fact that malaria itself frequently leads to abortion. Fieux reports the case of a woman, in the seventh month of pregnancy, who manifested, during a paroxysm of quotidian fever, a bloody discharge, and complained of pains similar to labor pains. Quinin cured the paroxysm and the premature pain ceased.

The hemoglobinuria following quinin has already been thoroughly discussed in other places. We may add that after large doses of quinin albuminuria is sometimes observed, and an existing cystitis may be made worse.

According to Osler, quinin is by no means contraindicated in malarial hemorrhagic nephritis; on the contrary, it acts quite as successfully and harmlessly as in other cases. Binz recommends the following in case of poisoning:

"Artificial respiration by rhythmic pressure over the region of the heart, in order to irritate this organ at the same time; hot baths (39° C.) with cold douches; internally, hot strong coffee or tea, and probably atropin. In cases calling for large doses of quinin the physician should ask himself whether any contraindication exists in the shape of pulmonary or cardiac weakness."

SUBSTITUTES FOR QUININ.

In addition to the modern invaluable antipyretics, a large number of drugs of vegetable, animal, and mineral origin have been recommended, sometimes empirically, again on hypothetic grounds. But so far none of them can lay claim to general recognition, although, on account of the intolerance manifested by many individuals to quinin, it would be very desirable to have an effective substitute.

In proving the antimalarial properties of a drug, great caution must be exercised. It must not be forgotten that our mild malarial paroxysms frequently recover spontaneously after the patient is put under better hygienic conditions, and that even infections with parasites of the second group have been observed to pass over without medication. The antimalarial efficiency of a drug, therefore, can be demonstrated in a severe malarial region only by an experienced observer.

In spite of the deficiency in our remedies we intend to discuss several which possess some, if only a slight, antimalarial effect, since under circumstances a trial of remedies other than quinin becomes obligatory. We refer to cases in which quinin has proved ineffective after long administration, and ones manifesting an intense idiosyncrasy against it (hemoglobinuria, etc.).

We turn first to the other substances obtained from Peruvian bark which show a similar composition to quinin. These are cinchonin, cinchonidin, chinidin, and chinoidin. Of these four, *cinchonidin* alone appears to be of value (Spitzner), though many writers, like Marty, condemn it. According to Marty, three or four times the dose of cinchonidin acts less efficiently than a simple dose of quinin, not to mention the fact that it is much more toxic. De Brun, on the contrary, obtained very satisfactory results from its sulphate.

Cinchonidin hydrobromate or hydrochlorate may be employed. Both are soluble in their own weight of water.

Cinchonin and *chinidin* are more questionable in their effect and more toxic than cinchonidin. They are, therefore, best avoided.

Euchinin, the ethyl carbonate of quinin, has been lately recommended by von Noorden. In solution it reacts alkaline. The hydrochlorate is readily soluble in water and has a very repulsive taste; the base and its tannate are soluble with difficulty and manifest only a slightly bitter taste. Euchinin is useful when children and the especially susceptible are concerned. It is readily administered in milk, cocoa, etc. On account of its slighter solubility, a dose double to that of quinin should be given. I have tried it in two cases of mild malaria with satisfactory results. Panegrassi and Conti have had good results in 20 cases. They claim to have observed no bad effects.

Cuprein, Chinæthylin, Chinopropylin.—These substances have been abstracted by Laborde, Grimaux, and Bourru from *China cuprea.* Cuprein is an alkaloid of which quinin is the methyl ether (Grimaux and Arnaud).

The formulæ of the whole series are:

$C_{19} H_{21} NOOH$	cuprein.
$C_{19} H_{21} NOCH_3$	quinin (methylcuprein).
$C_{19} H_{21} NOC_2 H_5$	chinæthylin.
$C_{19} H_{21} NOCH_3 H_7$	chinopropylin.

In experiments on malarial patients it was found that cuprein was less, the other two more, effective than quinin sulphate. The relations were:

Cuprein	2.00
Quinin	1.00
Chinæthylin	0.70–0.75
Chinopropylin	0.50–0.60

Chinopropylin showed associated toxic effects (tinnitus aurium, vertigo, nausea); cuprein and chinæthylin showed not any or at most very slight toxicity. The results of these investigations demand other experiments. The dose is evident from the foregoing figures.

Phenylchinaldin, a derivative of quinin, has been recommended by Tappeiner on account of its intensely poisonous effect on infusoria.

With amounts of 0.8 and 1.5 gm. pro die no unpleasant effects were noticed. The paroxysms were suppressed for a few days, but returned again, even under continued administration of the drug. The parasites did not disappear from the blood.

Among the phosphins, *methylphosphin* and *dimethylphosphin* were suggested by experiments of Tappeiner. They were administered in daily doses of 1 to 1.2 gm. Their effect was also only transitory (see Tappeiner, Grethe, Mannaberg). The failure of the quinin derivatives and the phosphins is of considerable theoretic interest. It would appear that quinin had, in addition to its general poisonous action on protozoa, a special property which made it capable of acting on the parasites inclosed in corpuscles within the circulation.

Phenocoll hydrochlorate has been administered with success by several investigators (Albertoni). Pucci had, among 20 cases, 17 cures, 2 undetermined, and 1 negative result. He employed it in some cases in which quinin had failed. Two cases of quinin hemoglobinuria were among those that were cured. Injurious associated effects were not observed.

Pucci gives the drug in doses of 0.15 to 0.25, four to five hours before the paroxysm. Throughout the day he gives 0.5 to 1.0 or even 2.0 to 2.5, and to children, 0.5 to 0.75. The remedy must be administered four to six days in order to be effective. Negative results have likewise been reported (F. Plehn, Geronzi).

Analgin has been recommended by Raimondi. Moncorvo obtained good results in children with daily doses of 0.25 to 0.30. Even the youngest children bore the drug well.

The dose for adults is 1.5 to 2.0. Analgin is insoluble in water and is consequently administered in powder form. Long continuous treatment with it is not advisable, since we cannot explain the red color of the urine which accompanies it.

Antipyrin and *antifebrin* act only symptomatically. Register recommends their exhibition before quinin, since quinin acts better during apyrexia, when it destroys even the crescents (?).

Methylenum cæruleum purum (methylene-blue) was recommended by Ehrlich and Guttman. It has been frequently experimented with, sometimes with satisfactory (Bourdillon, Röttger, Fereira, and others), again with unsatisfactory (Kétli Mya, Plehn, and others) results. It must be chemically pure, and should be administered in capsules in doses of 0.1 gm. The daily dose for adults is 0.5 to 0.8; for children, 0.25 to 0.5.

Soon after taking, the urine becomes yellowish green, later intense blue. As associated effects, vomiting, diarrhea, and strangury have been sometimes observed. In order to avoid the last it has been recommended to give, at the same time, several knife-pointsful of powdered nutmeg.

Ehrlich and Guttmann were induced to try this remedy on account of the election shown by the malarial parasites for it in the staining of preparations. On administration no evident staining of the parasites in the circulation takes place (Laveran).

Although methylene-blue has not yet proved itself a positive antimalaricum, it may be recommended for trial in case quinin fails or is for any reason contraindicated.

The same may be said of sodium salicylate, which has been sometimes successful. Vincenzi reports a case of quartan lasting nine months which eventually yielded to it. Quinin could not be employed on account of quinin hemoglobinuria.

Arsenious acid has also been recommended (Boudin). It is employed at present in the treatment of the cachexia and gives excellent results.

Recently Du Cazal has come forward for Boudin's method. He administers, in rebellious fevers, 50 gm. of the sol. Boudin (acid. arsenios., 0.05; water, 500) pro die, in doses of 20 drops in water every fifteen minutes. After three to five days this dose is exhibited every half-hour continually for about two weeks. Boudin himself gives 100 to 300 gm. pro die; after cessation of the fever, 100 gm. on the days of the paroxysm.

Subcutaneous injections of *bichlorid of mercury* have been recently recommended by Feletti for obstinately recurring cases.

Tannic acid has been lauded by Alix. It is administered on an empty stomach in increasing doses of 1 to 4 gm. in water pro die. According to Alix, this was successful in four cases in which quinin failed.

Tincture of eucalyptus globulus is claimed to be sometimes effective. It is employed especially in chronic cases, and then particularly for the neuralgic pains. Daily dose, two to four teaspoonsful.

Pambotano has of late been praised by Valude. It is obtained from the bark of a small leguminous plant—*Calliandra houstoni*—growing wild in Mexico, but cultivated as an ornamental plant in England. According to Valude, 70 gm. of the bark in the case of adults, 35 gm. in the case of children under twelve years, are added to a liter of water, boiled to 500 gm., and filtered. The color of the decoction is blood-red. This amount is divided into four portions and given warm with a little sugar. Villejean was unable to demonstrate an alkaloid in the bark. Valude treated eight cases with success. As associated effects, nausea and vomiting may be mentioned. Crespin also recommended this drug.

Calaya, a leguminous plant, was employed by Maurage with success in nine cases in Madagascar and Tongking.

In addition to these remedies, the great majority of which are questionable, there are many others, like sulphurous acid, potassium iodid, alum, carbolic acid, strychnin, helianthus, spiders, and cobwebs, the value of which is *nil*.

The remedial treatment of malaria before the introduction of quinin is of considerable interest. A full account is found in Morton, which merits particular attention on account of the critical acumen of the author. Morton praises antimonium diaphoreticum, sal. absynthii, and a mixture composed of the following bitters: Folia matricariæ, carduus benedict., comar. absynthii summit., centaur. min. flor., flor. chamœmel., to which were added semin. card. benedict. citr. and sal. absynthii. He apparently obtained good results, especially from antimonium diaphoreticum.

Finally, in malarial regions, the inhabitants make use of certain *household remedies*, to which even less effect can be attributed. The most commonly used are decoctions of lemons, different kinds of pepper, especially mixed with brandy, etc.

Hydrotherapy.—Attempts have been made to treat acute malaria by hydrotherapy. Currie stated that he had several times prevented the recurrence of a paroxysm by douching the region of the spleen with cold water. Priessnitz combated intermittent fever by cold water internally, cold frictions during the chill, frictions in a half-bath during the hot stage, and wet-packs during the interval. The greatest enthusiast for the hydrotherapeutic treatment of malaria was Fleury. He gave, one to two hours before the paroxysm, a general filiform douche of 12° to 14° C. (54°-57° F.), and simultaneously a strong filiform douche 3 cm. in diameter over the spleen, and claims to have obtained excellent results. Subsequent experiments proved also encouraging. Still, at the present day we can consider all attempts to replace quinin by hydrotherapy as futile; though it is not to be rejected as a symptomatic auxiliary, but, on the contrary, recommended especially in cases with hyperthermia, nervous depression, algor, etc., in which it acts as in other acute infectious diseases.

SYMPTOMATIC TREATMENT OF THE ACUTE INFECTION.

In addition to the specific treatment, which is indispensable, opportunities for symptomatic therapy frequently arise on account of tormenting or even threatening individual symptoms. It is not our intention to consider all the possibilities that may occur, since the great majority of them are influenced by the same therapy as in other diseased conditions. We will confine ourselves to certain symptoms peculiar to malaria, the combating of which requires special experience. As a first principle applicable to malaria, as well as other feverish conditions, the patient should remain in bed during the period of the fever. In cases of mild intermittent the patient may be allowed to leave the bed after the termination of the sweating stage, while convalescents from severe infections, with advanced anemia, should remain in bed until strength is sufficiently restored.

During the cold stage warm cloths and hot bottles help but little the subjective complaints; nevertheless, as a rule, we apply them. Of more value at this stage is opium, per os or in suppository. In an especially violent chill a morphin injection may be given. Hot drinks, like tea and lemonade, are allowable only when no nausea exists.

During the hot stage an ice-bag to the head, or, better, a Leiter's coil, is beneficial. In case of a continued fever or a hyperpyretic temperature cold packs and baths are to be employed as in other infectious diseases.

In case of subnormal temperature, as in the algid forms, a protracted warm bath with massage is indicated. To the bath may be added mustard or fir-wool extract. Other things strongly recommended are frictions with warm cloths, spirits of camphor and other aromatic substances, applications of sinapisms and other counterirritants to the calves, to the back, and to the epigastrium, together with injections of camphor and ether. It is unnecessary to mention also warm drinks.

The sweating stage demands no special treatment. In case of a sudorific pernicious, we may endeavor to control the profuse sweat by washes of acetic acid or other spirituous lotions. Opium, likewise, is of service.

The gastro-intestinal tract was and is even yet of considerable importance from the standpoint of symptomatic therapy. The majority of old physicians administered at once, "in order to cleanse the prima via," emetics and purgatives without regard to the manner of the infection or the severity of the attack. We only agree with the experienced physicians of to-day when we declare this procedure entirely superfluous and sometimes even harmful. Intestinal activity should be regulated in the same way in malaria as in any other infectious disease. Irrigations and saline purgatives in suitable cases meet these indications fully. Whether it is justifiable to give calomel under all circumstances in bilious remittent, as several modern physicians hold, is questionable. It may be that the polycholia, which in this form, as in hemoglobinuria, is usually marked, demands a more rapid evacuation of the intestine, yet in the majority of cases diarrhea occurs of itself and fulfils the indication.

Torti placed but little reliance on purgatives, and even believed that they might do injury: "Quamobrem ea certitudine qua febris per Chinam Chinam expellit eadem pariter per Cathartica revocatur."*

Tropical physicians, especially in India, still adhere to the administration of drastics "in order to relieve the circulation in the liver and spleen." According to Fayrer, there is given, in ordinary intermittent fever in India, a drastic, like colocynth, calomel, or jalap, followed by a saline purgative and 0.20 quinin in a bitter infusion. This is repeated several consecutive days. If gastro-intestinal irritation is manifest, instead of the drastic, ipecac, 1.0 to 1.2, is given.

They claim that quinin acts better after this treatment, though we may say that we do not appreciate the rationale of it.

In India malarial patients are given, besides, *Aconitum heterophyllum* (there called "Atees"), to fulfil what indication we do not know. In severe vomiting and gastralgia sinapisms to the epigastrium or even the hot iron itself, chloroform water internally (see treatment of blackwater fever), or chloral by clyster, iced drinks, cold irrigation of the intestine, and injections of morphin are serviceable.

Fayrer recommends Warburg's tincture; Rangé prescribes cocain:

℞. Cocaini muriatici	0.15
Aquæ laurocerasi	8.0
Aquæ	100.0

To be taken ice cold, a teaspoonful at a time.

The same measures may be employed in singultus. Diarrhea is combated in the usual way.

On the part of the lungs, the dyspnea sometimes requires attention. Inhalations of oxygen or injections of morphin are probably the most useful.

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* *Loc. cit.*, i, Cap. vii, p. 60.

In coma the bowels and bladder should be evacuated. Counter-irritation is indicated. In robust individuals leeches may be applied to the mastoid process, especially if there is congestion in the head.

On the west coast of Africa the favorite remedy for relieving the diuresis in blackwater fever is Kinkélibah. This is a plant, the bitter-tasting leaves of which are made into an infusion. The dose is 4.0 of the pulv. fol. Kinkélibah in 250 of water, administered cold.

For pain in the splenic region dry cups, or, in the case of robust individuals, several leeches, may be applied; for pain in the liver, cataplasms.

In heart-failure subcutaneous injections of caffein, camphor, and ether, and digitalis by clyster or by the mouth, are recommended. Venesection should practically never be done. The very few cases in which it is indicated have been described in the foregoing section.

Transfusion of defibrinated blood in severe exhausting infections is of great utility and deserves trial. It has saved many a life (Oré). Salt infusions (subcutaneously) are also recommended, especially in the algid, choleraic, and hemoglobinuric forms.

The employment of alcohol demands consideration. Experience shows that it is not so well borne as, for instance, in typhoid fever (Marandon de Montyel). In the tropics it should be administered with great caution. The rule may be laid down to omit alcohol entirely as long as the malaria is not of an asthenic, algid character, when rum, brandy, champagne, etc., are called for.

In case of obstinate relapses of intermittent, as well as after recovery from a pernicious attack, a change of climate is to be insisted upon, since it is the only way in which to protect the individual from new infection and cachexia.

In tropical countries the military occupants have erected sanatoriums at highly located points, in which convalescents may recuperate. These sanatoriums are undoubtedly of great value, but they cannot be made to replace repatriation. Another feature of these countries is the ship sanatoriums. Further information in regard to them will be found in Catrin's work on "Chronic Malaria" and in Kohlbrügge's publication. This latter also gives valuable advice in relation to the choice of suitable places for sanatoriums.

TREATMENT OF CHRONIC MALARIA AND CACHEXIA.

In the treatment of chronic malaria and cachexia the principal rôle is played by residence in a healthy climate, good nourishment, quiet life, moderate exercise, and baths. The remedial treatment is secondary. Frequent examination of the blood is indicated in order to show existing infection. If ameboid parasites are present, quinin must be administered from time to time.

The combating of the anemia by iron and arsenic is also very important. The choice of preparation depends usually on individual circumstances. Nevertheless, we recommend especially Blaud's pills and ferratin, and of the arsenic preparations, Fowler's and Pearson's solutions. They should be given under ordinary precautions.

Under great precaution, especially as regards the liver, alcohol may be given to old malarial patients, though it is usually best avoided.

If the syndrome of progressive pernicious anemia is present, an endeavor should be made to check it by absolute rest, a sea-voyage, light massage, arsenic, and milk diet. According to Fayrer and Ewart, iron is badly borne in these cases. In addition, bitters may be employed to encourage the appetite, preferably, tincture of cinchona, cinchona wine, quassia amara, or calumba. Bitters should be administered before meals.

The mineral waters, the saline and alkaline-saline, have also been employed with advantage. Carlsbad, Marienbad, Vichy, Wiesbaden, and Kissingen are the most frequently sought health resorts. In cases of severe anemia the waters containing iron and arsenic are to be preferred, as Franzensbad, St. Moritz, Elster, Schwalbach, Levico, Roncegno, La Bourboule, etc.

Organotherapy.—Critzmann recommends, in cachexia, bone-marrow and spleen. In four cases with splenic tumor, edema, etc., he claims to have had good results, which were manifest in two to four weeks. He gave at every meal the following mixture in an uncooked chopped condition:

Beef-spleen	50 gm.
Bone-marrow	10 gm.
The yolk of one egg.	

Hydrotherapy is often very useful in cases exhausted by a severe attack. Too cold water and too brusque measures should be avoided, and lukewarm baths, cool frictions, rainwater douches, etc., be given the preference. Severe, even fatal, malarial relapses have resulted from the application of the cold pencil douche to the splenic region (Fazio, Ascoli). The same is true of massage. Carried out carefully, it may be of the greatest service in assisting nourishment and improving the general condition; otherwise it may result in injury.

Papinio observed, in three cases of chronic malaria, forty-eight hours after massage of the spleen, a renewal of paroxysms and the reappearance of parasites in the blood.

Among the hygienic regulations, residence on the sea must be mentioned first. Cold sea-baths may be allowed as an experiment in light grades of anemia; in severe cases they are decidedly contraindicated, though warm sea-baths are always to be recommended. High mountain air acts likewise very beneficially, yet excessive exercise, especially exhausting tours, must be avoided.

The nourishment should be mixed, simple, and sufficient. Substances that act as irritants on the intestine and liver, as all kinds of spices and alcohol, are to be eschewed.

When the splenic tumor causes disturbance and pain on account of its size or perisplenitic inflammation, the question of extirpation may be forced on the physician. Before pronouncing for it, every means, like drugs, hydrotherapy, and electricity, should be tried to lessen the size of the tumor. The usual failure is explained by the anatomic structure of the ague-cake. The measures that have been recommended are:

Quinin.—As important as this is in lessening the size of the acute splenic tumor, so insignificant is it in the chronic tumor. Berberinum sulphate has been repeatedly recommended. Arzela states that he observed rapid diminution in size after morning doses of 0.5 dissolved in warm water. As associated effects he mentions mild stupor, epistaxis, more rarely diarrhea and vomiting.

Injections, into the parenchyma of the spleen, of quinin, Fowler's solution, phenol (Mosler), quinin (Fazio), ergotin (Messerer), phenocoll (Micheli), and sterilized water (Murri and Boari) have been recommended. The results are variable. We must also add that these injections are by no means without danger. Osler observed one case of internal hemorrhage after puncture of the spleen.

Among external applications we may mention the ice-bag, the ether spray (Moscucci), the actual cautery, leeches, sinapisms, and vesicants. In splenic pain these procedures are often quite successful.

Parona recently reported that he employed with good results daily subcutaneous injections of 1.0 of a potassium iodid solution (iodi puri, 0.25; potassii iodati, guaiacoli āā 2.50; glycerini puriss. steril., 25.0).

Cold douches and electricity have also been recommended, though the results leave much to be desired. It must not be forgotten that a too brusque procedure may bring on new paroxysms of fever.

Laveran's suggestion that a dose of quinin be administered previous to a strong douche should not be disregarded.

Fayrer recommends the application, to the splenic region, of an ointment of the red iodid of mercury, while the abdomen is exposed to the sun or a fire. In Bengal the following "spleen mixture" is employed: Pulv. jalapæ, rhei, calumbæ, zingiberis, potassii tartaric., āā ʒj; ferri sulph., gr. xx; tinct. sennæ, ʒiv; aquæ menthæ sativæ, ℥x. Sig.: The tenth part twice daily. Fayrer praises very highly sulphate of iron with quinin.

Splenectomy has been repeatedly done in chronic malaria, sometimes on account of general disturbances produced by the splenic tumor, again, on account of torsion of its pedicle, and frequently with good results. Recently splenopexy has been tried. The chances of splenectomy improve the longer the pedicle and the fewer the adhesions to complicate the operation. After Wyman's experience we must warn about ligation of the splenic artery. The technic of the operation will be found in surgical works.

PROPHYLAXIS.

Setting aside the great advance that has accrued to our knowledge since the discovery of the connection between mosquitos and malaria, yet even prior to this there were few infectious diseases so thoroughly under control in regard to their avoidance as malaria. It was the cultural activity of the race that converted severely infected, death-dealing malarial foci into salubrious, thickly inhabited territories, and it was the devastations of barbaric hordes that changed these fertile fields to their original condition.

The general prophylaxis of malaria could, up to the discovery of the mosquito-malarial cycle, be stated in the one word, "cultivation," and this, in a sense, is still true. It will be well, then, to recall here some of the older examples, based as they were on practical experience, and then to discuss how the matter now stands in the light of our present knowledge. The basis of malarial prophylaxis consisted in the rendering of the soil unsuitable for the development of the parasite, as it was then thought, but as we now know, the unsuitability refers to the development of the mosquito.

This problem may be easy or difficult, even impossible, according to the circumstances surrounding individual cases.

It was a very different matter, for instance, to change the condition of a limited malarial focus in the midst of a thickly populated rich country, and do the same for an extensive, thinly populated, impoverished malarial district. A highly situated, easily drained swamp offered scarcely any difficulties, while a district covered here and there with brackish water, and lying on or under the level of the sea, might have presented insurmountable ones.

It is not our intention to discuss *in extenso* these different methods for improving the "sanitary" condition of the soil. This is the work of the hygienist and the sanitary specialist. For detailed information we can recommend the monumental work of Fichera. Still, we may say that all these old and well-tried methods had this common aim, the regulation of the ground moisture so as to promote fertility.

The following measures seemed to the earlier school of hygienists particularly important: The walling-off of the sea or rivers in order to avoid flooding, the separation of fresh from salt water in order to prevent the formation of brackish water, canalization, drainage, the filling up (colmata) of deep-lying basins, and the refilling of ditches opened up in ground working (especially the building of railroads).

Exceptionally during severe epidemics radical measures were undertaken, as, for instance, the copious flooding of malarial foci. This was first put into practice by Empedocles, later by Lancisi.

These regulations were to be accompanied by cultivation, without which the end was rarely attained. It was, as it seemed, necessary to bend the malarial soil to the yoke, and exhaust its strength in a useful way, in order that it might not be employed in the production of miasmata. The ground could not be left as a pasture, but had to be systematically planted with grain, sugar-cane, eucalyptus, etc. The special properties of the soil and the climatic conditions of the locality decided the choice of plant. These hygienic regulations occasionally produced extraordinary results.

It was evident that the turning-up of the earth necessarily associated with sanitation caused a considerable sacrifice of capital and human lives. Every movement of the soil in malarial region appeared to carry with it the greatest danger for the laborers. Enormous loss of life had, for instance, resulted from the building of railroads through malarial foci.

In the summer of 1805 the La Chartereuse swamp near Bordeaux was drained. The result was 12,000 cases of pernicious fever, with 3000 deaths. According to L. Colin, there were 109 deaths from pernicious fever in the year 1881 in the Arrondissement Bastia among the railroad laborers and wine-growers.

Sanitary measures have been carried out in all the civilized countries of the world. We may recall the number of endemic malarial foci in Germany, Austria-Hungary, England, France, and Holland, even at the middle of this century. The steady development of hygiene, the increase of the population, and the improved condition of the people, as well as the advance of industry, have bestowed immunity on districts and territories infected for centuries. A glance into the publications of older writers demonstrates the difference between then and now. Formerly the cases were innumerable; now they occupy but a very small space in medical literature. Berlin, Vienna, Prague, and other large cities all showed then pernicious malaria, while now they show only a few mild cases of intermittent.

Drainage and canalization accomplished magnificent results in

Ireland, England, Austria, Holland, and North America. In Austria, Pola was an instructive example. At the present time it is a growing town, the principal harbor of the Austro-Hungarian marine, and shows a very small morbidity from malaria, while a few decennia ago it was notorious and dreaded. The drainage and canalization of the Prato grande and Piccolo, the conversion of this desolate waste into a maneuvering-ground, and similar regulations, carried out on Jilek's proposal, were the agents by which the rapid results were produced. This is evident from the fact that an inadvertent obstruction of the drainage-canal was sufficient to allow a renewed outbreak of the endemic, though this was soon interrupted.

The building of dams has also contributed more or less in all civilized countries to the combating of malaria, though to the greatest extent in the Netherlands. Swamps were laid dry, especially in Holland and Italy. The delta of the Tiber and the Ostian swamp have been, after considerable effort, regulated and in part drained, with the result that a diminution in the cases of malaria has been obtained.

In swamps where drainage was impossible a regular level was aimed at, especially during the summer months, by the regulation of the incoming and outgoing water, and by the building of dams, since it was not the surface covered with water, but that which was alternately under water and exposed to evaporation, which was dangerous.

By colmata (Italian; *Kolmatage*, French), for instance, was meant the filling-up of deep-lying ditches or basins for the purpose of sanitary improvement and bonification. This is seldom done directly for the sake of husbandry (*colmata arteficiale*), but usually by permitting an inflow of water from the next stream or the sea, which is allowed to sedimentate, and repeating the process until the required level is reached. The process is naturally slow, and requires decennia for its accomplishment. The most extensive achievements of this kind have been carried out in Italy. Historically famous is that of the Val di Chiana, between the Tiber and Arno, the colmata of which was attempted under the Medici (1525), but successfully accomplished only in this century. We may mention, besides, the Tuscan Maremma. The same has been done in England and Holland with sea-water.

The cultivation of the ground from this, the old standpoint, might be designated as a second important factor in prophylaxis. It was well known that when cultivation is neglected even healthy regions pay the penalty of infection. The extensive clearing of forests especially has drawn in its wake serious results for the neighborhood.*

For the purpose of sanitary improvement the most useful plants are those which grow rapidly under the existing climatic and geologic conditions, though naturally the monetary value cannot be left out of consideration.

At one time the *Eucalyptus globulus* and *Eucalyptus rostrata* acquired considerable reputation. There are many instances where very successful results were accomplished by the planting of eucalyptus trees, as in the vicinity of the Trappist monastery, Tre Fontana, near Rome, certain localities in Algeria (around Bona, Philippeville) and in Corsica. *Eucalyptus rostrata* has recently displaced *Eucalyptus globulus,* on account of its greater adaptability to different soils and its resistance to extremes of temperature.

In addition to the eucalyptus tree, pines, *Helianthus annuus, Acorus calamus aromaticus,* have been recommended. Vincent and Burot laud especially the *Coniferæ filao* (*Casuarina equisetifolia*), which has been tested at Bourbon.

It is probable that the beneficial effects of these plants has been exaggerated, and that the improvement following the planting is due to concomitant alterations in the surface-level of the soil, rather than to a drying-up of the ground on account of their quick growth and rapid evaporation. Unfortunately, this method, even if we grant all that has been claimed for it, is capable of improving only relatively small areas, and is of no importance in the case of immense stretches of malarial region, such as are found in Africa.

In addition to these general prophylactic measures, which were applicable to whole countries, we must consider, too, the special forms of prophylaxis which were adapted to narrower spheres.

There were cases reported in which infection took place on ships, when the holds, bunks, bilges, etc., were neglected, and we have already referred, on page 37, to the question of infection in dwelling-rooms. Although these cases were not absolutely determined to be malaria, the possibility of such confined foci was not beyond question. The prophylaxis consisted in keeping clean and preserving dry the ship's compartments. The question also arose whether or not the improvement of the drinking-water was to be considered under the head of malarial prophylaxis.

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* The clearing of woods was apparently especially responsible for the infection of the Roman Campagna. From more recent times Mauritius (Île de France) is another good example. Humboldt and Darwin found the island salubrious and flourishing, while, since 1867, the severest forms of malaria have raged as a result of clearings in order to establish sugar-plantations. The removal of the trees, it was thought, was associated with a diminution of precipitation, and this allowed the river-banks to become marshy with brackish water (Pellerau). [Whatever the influence of this factor, the result is now clearly attributable to the formation of numerous collections of water in which anophelines can multiply almost indefinitely.—Ed.]

There were not a few examples, especially from American forts (see Rupert Norton), where the introduction of the best spring-water altered not in the slightest the malarial endemic. On the contrary, Fayrer asserted that good water was the first essential in malarial prophylaxis.

Individual prophylaxis, moreover, comprehended all the regulations capable of protecting the individual from infection.

It was naturally easier to find protection in a city of which only the periphery was malarial, than in the country in the midst of a severe malarial focus.

Experience taught that in cities the most thickly populated streets (therefore, as a rule, those situated centrally) are most immune, while the peripheral lying parts, furnished with ornamental and other gardens, villas, ponds, etc., are most frequently infected. In such cities it was, therefore, recommended to choose the central portion for habitation. The dwelling, it was thought, should not lie deep, nor yet be situated too high; the height of an ordinary second story seemed best. If it was necessary to occupy the first story, the bed was raised as high as possible from the floor. Moreover, it was always thought by many advisable to protect the bed by a mosquito-netting [a practice which is now the pivot and basis of personal hygiene, but it is no longer the unseen miasm that is screened off, but the seen mosquito.—Ed.].

L. Colin, in a series of notes on the protection of workmen in malarial regions, mentioned the following points as the most important:

1. Excavations should be done piecewise, in order that too much earth may not be turned up at one time.
2. The laborers should come from the region in which the work is done. Only the robust and healthy should be employed.
3. Machines are to be used as far as possible.
4. The work should be interrupted during the months of July, August, and September. If the work does not permit of postponement, it must be done during these months only by day.
5. The laborers should pass the night in camps or be quartered

in caserns. The latter should be removed as far as possible from the working-place. The windows should be hermetically closed before evening. Tents should be rejected.

6. Morning and evening fires should be lighted at the working-places.*

7. Clothing should be flannel.

8. Drink should be good water; if this is wanting, tea.

9. In the morning, before beginning work, a warm meal should be taken (tea, bouillon, coffee).†

10. In the warm season, 0.5 to 1.0 quinin pro die should be taken as a preventive.

The neglect of these rules produced frightful results in many an army. We may recall the occupation of Walcheren by the English in 1809. The troops, numbering 50,000 men, were landed in August,—in other words, the worst season of the year,—and, as a consequence, were decimated.

The English expedition to the gold coast of Guinea (1874) succeeded much better. At the advice of the physicians the troops were allowed on land only during the month of January. The morbidity was insignificant. As a tribute to the medical men this expedition was called "The Doctor's War."

The previously mentioned Ashanti expedition of the English in 1895 was also magnificently conducted. The 3000 troops were landed in March, on account of it being the healthiest month. Prepations had been made so that the troops started for the interior without spending an hour on the coast. This was accomplished by the previous laying-out of a road by the natives and the building of suitable shelter along the way. The 3000 soldiers had at their disposal 12,000 natives to carry their ammunition, baggage, etc. As a consequence, among the 3000 only 17 fell ill. How many of the natives succumbed in making the preparations has not been stated.

The French expedition to Madagascar (1895) showed frightful losses on account of the long, unnecessary sojourn of the troops on the coast.

Sanatoriums, Villes de Santé, Health Cities.—The civilized countries of Europe now erect stations in their tropical colonies to serve as refuges during the unhealthy parts of the year for the white officers, merchants, soldiers, etc. In the laying out of such stations highly situated places are chosen, provided, of course, these manifest no other hygienic disadvantages. Well-known places throughout India are Simla, Darjiling, and Outakamund, although there are numerous others in the process of development. We may also mention in Ceylon, Kandy; in Java, Salatiga and Tosari; in Jamaica, Hope Gardens and New Castle; in La Réunion, Salazie. In the case of ships' crews, a return on board before twilight was advisable. The sleeping on board at night was one of the best means of prophylaxis.

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* It was noticed by Lancisi that brickmakers remained immune in the midst of malarial regions.

† Lancisi insisted on no exercise in the open air on an empty stomach, "Quare consultatissimum erit jentaculum (breakfast) sumere vel antequam fenestræ aperiantur."

REMEDIAL PROPHYLAXIS.

For a long time the endeavor has been made to prevent malaria by the use of quinin, and numerous are the expressions of opinion in regard to the results. The majority contend that a systematic continued employment of quinin diminishes the number and severity of the cases; for instance, Bryson, van Buren, Jilek, Gestin, Thorel, Bizardel, Groeser, Laveran, Vallin, Saint-Macary, and others. Among the opposition we may mention Le Roy, Navarre, Reynaud.

The conviction is at present quite general that quinin is a preventive, and occasionally German, French, and English troops in malarial regions come out morning or evening, or both, for the "quinin parade," but it is rarely that this parade is carried out with strict supervision, and all kinds of expedients are adopted to avoid the bitter draft.

For instance, Jilek reported the following experiments from Pola: Among 736 men, 500 were given about 0.17 quinin pro die, in a glass of rum, from June 1 to September 20. Among these, 18.2 per cent. fell ill; of the others, 28.8 per cent. A number of instructive examples are presented in Bizardel's thesis.

Quinin appears to act prophylactically by destroying the parasites that gain entrance to the blood or by hindering their development. In other words, the parasites find in the blood conditions unfavorable to their existence. Bearing this in mind, it is evident that little or nothing could be accomplished with doses of 0.10 to 0.20 pro die. We, therefore, agree with Laveran that the smallest daily dose worth giving is 0.50. In order to avoid, as far as possible, the disturbances caused by the quinin, the evening hours are to be preferred for administration. A dose of 0.5 should be taken at least every second evening, in powder form, in solution, or in pills.

This precautionary measure is recommended to every one who finds himself in a malarial region at the time of an endemic. It should be continued several days after leaving the region in order to destroy any organism still remaining.

The prophylaxis by means of arsenic possesses only isolated defenders, as Tommasi-Crudeli and Gouvéa, and the results of others are so little encouraging that the method cannot be recommended.

Prophylaxis by means of respirators is now of historic interest only. The idea of freeing the inspired air from germs is an old one. Lancisi recommended the washing of the nasal cavities, forehead, and ears with spirits of camphor and rose vinegar, and the constant retention before the nose of a small sponge moistened with acetum theriacale. He likewise warned against swallowing the saliva, since it might be contaminated by inspired germs. The wearing of masks in which a layer of cotton filters the inspired air was recommended by Heurot and Zemanek.

Attempts at immunization were made by Celli and Santori by injecting six healthy persons with the blood-serum of a buffalo, a goat, and a horse, from the region of the Pontine marshes. After 130 c.c. of serum had been injected, Celli and Santori inoculated three of the persons with blood from a patient with quartan fever, and three with blood from a severe estivo-autumnal case. The serum injections were continued in some, in others not. The three persons who were injected with the blood of the estivo-autumnal case were attacked within thirty hours, six and seventeen days respectively, while those injected with the blood from the quartan case manifested the disease in about twenty-five days. Since considerable quantities of blood were injected (1.5 to 4 c.c.), the incubation was much longer than is usually the case in persons not treated with the serum. (See Table I, p. 56.)

These investigators also inoculated a family of five persons living in a severe malarial region: three of the persons remained unaffected; one manifested a light attack, and one a relapse of an old infection. Though the experiments so far have given no satisfactory results, their continuation is desirable.

[It may be well to deal briefly here with the question of prophylaxis, which has assumed a somewhat different aspect, since our efforts are now directed by an exact scientific knowledge of the part played by anophelines in the transmission of malaria. Though our knowledge is based on universally accepted data, yet even now it is true that in the main the method of prophylaxis is the same, or at least not very different, from that practised for many a generation, viz., drainage of the soil. The only difference lies in the fact that our efforts are now directed toward eradicating or avoiding malarial mosquitos, while in the past they were directed toward eradicating or avoiding the "miasm" in the soil. It concerns the practical sanitarian or the hygienist, rather than the physician, to discover and carry out the best means of fighting the malarial mosquito. We would here indicate only some aspects of the problem, which are treated more fully in the appendix to this article, p. 206.

(1) Of mosquitos, it is only those of the subfamily *Anophelinæ* that transmit malaria, and even now we do not know if all of these, over 80 in number, do so. In fact, we can say this certainly of hardly ten. This lamentable gap in our knowledge will, no doubt, be soon filled up, but it at present exists.

(2) Other mosquitos, *e. g.*, those of the subfamily *Culicina*, *Aedeomyina*, etc., are quite incapable of transmitting malaria. It is true, moreover, that the breeding-places of these mosquitos are different from those of malarial mosquitos. Mosquitos of the genus *Culex*, *Stegomyia*, etc., breed in artificial collections of water about houses, such as water-butts, old tins, etc. It is necessary, therefore, in prosecuting a campaign against mosquitos, to bear in mind these facts, because a diminution in these latter is more easily brought about, and it is not sufficient to state that mosquitos have been diminished as the result of operations (drainage, emptying of water-butts, pétrolage, etc.) without clearly ascertaining whether the malarial mosquitos have been influenced. Of course, the sanitarian may attack mosquitos as a whole, and not consider the species present at all, but we do not think that a blind campaign of this sort is likely in the end to be most effective. Further, on the point of economy it may be doubted whether this is advisable, for evidence exists that not all even of the *Anophelinæ* are concerned in the transmission of malaria (see page 115). The methods by which mosquitos are attacked we cannot consider in detail here. They practically resolve themselves into—(1) Drainage, *i. e.*, doing away as far as possible with all breeding-grounds; and (2) pétrolage (as a temporary measure), *i. e.*, treating the breeding-places with tar, kerosene oil, or other larvicide. These methods are for the consideration of the sanitarian, and practically resolve themselves into a question of the money necessary to do away with small collections of water. We would only point out the difficulties attending the method where the water is that of an irrigation channel or flowing river with shallow,

weedy banks, or where, again, at one period of the year a river is a raging torrent, at another a sandy bed with innumerable separate collections of water in which myriads of larvæ occur, or again, where we have to deal with irrigated crops. We would, in conclusion, point out a means of prophylaxis carefully studied and earnestly recommended by Stephens and Christophers as the result of their close observation in tropical Africa and India. It is, in a word, "segregation." This method was designed to save the Europeans living in the deadly conditions of West Africa from the certain infection with malaria that must otherwise ensue sooner or later. As has been stated on page 208, it is the native that is the great source of malaria in the tropics. The native children are almost universally infected, and the European living in their midst is then infected by the anophelines, which occur in thousands in native dwellings. Now, it is very striking that where in West Africa Europeans live in bungalows well isolated from native dwellings (even a quarter of a mile away), they enjoy a marked freedom from fever compared with those who live with natives in native huts at their door. The official quarters at Accra (Gold Coast), and the recently constructed hill station for Europeans at Freetown (Sierra Leone), are a striking instance of the benefits of "segregation." It was well known at Accra before the mosquito cycle was discovered that this was the healthy quarter. Here the isolated bungalows are situated some a quarter, some a half, mile from any native village, and the result is in all respects excellent. The building of European quarters, the placing of an isolated colonist's bungalow away from the immediate vicinity of villages, is a policy which must be accompanied with a striking improvement in health, and many a valuable life be rescued. Such a policy can in many instances be effected with but little cost, and should, we believe, be adopted when drainage, which is expensive and which may not be carried out for years, is being waited for. By small alterations, often implying the destruction or removal of only a few native dwellings, we are convinced many a European life will be spared. It is a policy that, in its highest development, is almost universal in India, where the state of civilization and progress is far beyond that of tropical Africa; it consists in the existence of a European cantonment and a separate native bazaar, and be it merely a coincidence or not, the two main centers of blackwater fever in India are just those where these conditions do not prevail, but where the tea-planter or missionary is living surrounded by natives in whom endemic malaria exists to the extent of about 80 per cent. This policy, we have seen, is to benefit the European. It is justifiable on the ground that it is in the European that fever shows those pernicious and deadly effects to which so many lives are sacrificed in tropical Africa. The aim of prophylaxis in the end is to benefit the population at large, but in the tropics, where we have comparatively few Europeans living in the midst of a native community by which they are infected with malaria in its most deadly forms, it is surely in no selfish spirit of opportunism, but in a strictly justifiable spirit of self-preservation, instead of reckless exposure to known evils, that some measure of segregation should be adopted. We need only point out finally that segregation is equally applicable to the colonist isolated in some remote village, to larger settlements, such as mining and railway camps, and eventually to towns, for in towns, even small ones, we find that areas actually do exist which are free from anophelines, while the suburbs of such towns may be teeming with them.

With regard to mechanical prophylaxis by wire gauze, many examples have shown that efficient protection may be obtained in this way, but the fact should not be lost sight of that such measures can be only temporary.

We may add one word with regard to personal prophylaxis. The mosquito-net is absolutely indispensable, but if used in such a way that an anopheline is ever found inside, it indicates either a want of care or a want of intelligence on the part of the owner. It is possible to use a net in such a way that one may live with absolute impunity in the most highly infected regions. Finally, such adjuvants as thick clothing, gaiters, or mosquito boots for the legs and ankles are by no means to be despised. In a word, it is not too much to assert that the person who allows himself to contract malaria in the tropics is lacking in knowledge or intelligence.—Ed.]

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INFLUENZA AND DENGUE

BY

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EDITOR'S NOTE.

The seven years which have passed since the publication of Leichtenstern's book have not seen many essential additions to our knowledge of influenza. So complete is his description that even in the most modern text-book of bacteriology he is largely quoted.

The style, even in the original, is more of the lecture than the book type, is frequently highly idiomatic and at the same time condensed. Consequently it is not easy to translate well, and I regret having been unable to give so much time to the revision of the translation as I could have wished. I hope the addition of an index will be found useful.

It is a matter of regret that the gifted author has not lived to advise in the work of bringing his volume up to date and to see it published. The irony of fate decided that he should die of croupous pneumonia following influenza on February 23, 1901, at the too early age of fifty-four years.

ALBERT S. GRÜNBAUM.

THE UNIVERSITY, LIVERPOOL,
May, 1905.

INFLUENZA.

HISTORY, EPIDEMIOLOGY, AND ETIOLOGY OF INFLUENZA.

THE winter of 1889–90 is indelibly engraved on the history of great epidemics. An influenza epidemic greater than any before arose in the far East, spread like a hurricane through Europe, and thence over the greater part of the earth. Four decads after the last European pandemics (1847–48) the medical profession of our day found itself confronted by a new disease, which up to that time had been known to them only in the history of medicine. The interest which the affection everywhere elicited, the competition which it kindled in all civilized lands to apply to the new disease the progress and the acquisitions of modern medicine, advanced our knowledge of influenza in every direction.

Men became absorbed anew in the history of influenza and extended its study to a diligent examination of the oldest sources, as is shown in the excellent monographs of Ruhemann, Ripperger, and Kusnezorn-Herrmann. The classic essays of Most (1820), Schmeich (1836), Gluge (1837), Canstatt (1847), A. Hirsch (1860–81), Biermer (1865), Haeser (1876), Zülzer (1886), the important works of Peacock (1847) and T. Thompson (1852) in England, Saillant (1870) and Ozanam (1835) in France, Zeriani (1804) in Italy, received anew their well-merited recognition. The most important result of these historic researches was the proof that the last pandemic, both in its epidemiologic character and also in its clinical picture, symptoms, and protean variations, was identical with the influenza of former decads and centuries.

Epidemiologic investigation is much indebted for its progress to the accuracy of modern statistics, to the high development of medical journalism, and to the powers that have been universally brought to bear toward achieving collective investigations and scientific researches.

Among the important works of recent times the following may be mentioned: The German Collective Investigation Report, edited by A.

Geyder and S. Guttmann; the exhaustive reports on the epidemic of influenza (1889–92) of Parsons; the report of the French Academy by Proust-Brouardel, and the army report of Kelsch and Antony; the account of influenza in Russia reported by Teissier; the Belgian "Enquete sur l'épidémie de grippe"; the Dutch report of Wertheim Solomonson and de Rooj; the Danish report by Carlsen; the Swedish, by Cl. Linroth; the Egyptian by Engel-Bey, as well as reports of collective investigations from Australia, Massachusetts, Riga, Cologne, and Danzig.

Worthy of particular mention are the reports of the Imperial Board of Health in Berlin, containing the comprehensive compilation of the statistics of the German Empire regarding the influenza epidemic of 1889–90, by P. Friederich, and the epidemic of 1891–92 by Wutzdorff; the official report on influenza in Switzerland, 1889–94, by F. Schmid; and, finally, the report published by the Prussian War Office on "Die Grippe-Epidemie im deutschen Heere, 1889–90," and the "Deutsche Marinebericht," compiled by Elste.

The most important advance in epidemiology was the universal acceptation of the doctrine of the contagious nature of influenza, of its transmission from person to person, and its dissemination through human intercourse. These views, although supported by the older authors, were again and again disputed by the majority of physicians even up to and at the beginning of the latest pandemic. There is now an overwhelming amount of material, collected from every scource, placing this doctrine on a firm foundation.

One of the oldest supporters of the view regarding the contagion of influenza was Ch. Calenus (Greifswald), who in 1579 wrote: "Contagiosum dico Morbum, quia etsi quidem ab occulta quandem coeli influentia principaliter eum profisci hauo dubium est . . . eo in loco quo jam grassabatur inter homines citius eos invadebat, qu cum affectis frequenter conversabantur, quam eos, qui a consuetudine affectorum studiose abstinebant." But the real birthplace of the doctrine of contagion is England, where it was formulated upon facts, which will be discussed in detail later, by Haygarth, Hamilton ("cause not in the air, but in a specific contagion"), Gray, Hull, Duggard, Bardsley, and others, during the epidemics of 1775–1803. In addition we may mention among the supporters of the contagion theory Simonin, Lombard, Petit de Corbeil (1837), Blanc (1860), and Bertholle (1876). To Ch. Baümler (1890) is due the credit of disseminating the law of contagion through Germany.

The guiding science in the etiology of the acute infectious diseases, namely, bacteriology, solved the difficult problem of finding the specific cause of this disease only after repeated attempts and failures. Should the Bacillus influenzæ, discovered by R. Pfeiffer in 1892, continue to maintain in future pandemics its place as the exclusive cause of the disease, as may certainly be expected, its discovery may be considered as the most important achievement of our latest influenza pandemic. It remained for clinical and anatomic investigation to complete the structure founded by our ancestors, and to arrange it in accordance with the progress of science. The pandemic of 1889 was the first to occur in the period of specialism of modern medicine. For this reason many symptoms, complications, and sequelæ which had in former times been overlooked received now for the first time thorough investigation and recognition. In how high a degree the science of medicine performed its task, a glance at the almost boundless literature of influenza will show. The progress of recent years in epidemiology, etiology, and clinical medicine, already mentioned, makes it self-evident that we must employ the perfected experience of our latest pandemics as the foundation of our treatise. Nevertheless, we cannot entirely omit a retrospect to the history of former epidemics.

NOMENCLATURE OF INFLUENZA.

Medical writers previous to the middle of the last century described influenza under the name of *catarrhus epidemicus*, *febris* or *cephalæa catarrhalis epidemica*, *tussis epidemica*, *contagious catarrhal fever*. A disease which travels throughout all countries naturally receives numerous popular designations. Numbers of these names are very droll, and point to the harmlessness of the disease. But we will pass them over. The expressions "horion" (1411, in France) and "lightning catarrh" (1782) point to the sudden onset of the disease. The names "tac," "sheep's cough," "sheep's disease" (1580), were applied to influenza no account of the loud, bleating cough that characterized it. The names "Gallant" and "fashionable disease" (1709–32) were applied on account of its "newness" and because every one had to follow the fashion.

The designations Chinese, Russian, Spanish, Italian catarrh point to the supposed country of origin of the pestilence in each case. The name "coqueluche" was first applied (1578) to influenza; but later it was transferred to whooping-cough, and in this way has produced considerable confusion in the history of both diseases.

The term influenza (influxus) was first applied to the disease in the epidemic of 1743 by Pringle and Huxham. The word points to the causation of the disease, "influence of cold," *influenze di freddo*, or "influence through atmospheric phenomena." Even Ch. Calen (1759) makes it depend on "*ab occulta quadam coeli influentia.*"

The word "grip" originated simultaneously with the name "influenza" in the year 1743; but its birthplace was France, where, up to the present time, the disease has had only this enviably convenient name. The word is derived from "aggriper," to attack, or from "gripper," to catch, to snatch, and perhaps originated in an analogous manner to the words lightning catarrh and horion. The Slavonic form of the word (*chrypka* = hoarseness, J. Frank Eiselt) has not yet been proved to be an earlier name for the disease. Grant (1782) relates that the name is derived from an insect called "la grippe," which at that time in Europe was generally considered to be the cause of the disease (compare section on Influence of Meteorologic Conditions).

The suggestion to confine the term influenza to the "real epidemic influenza" and the term grip to the ordinary catarrhal fever comes much too late to have any chance of success, and would, moreover, make the international comprehension of the terms more difficult. At present everybody knows that the grip of the French and Belgians is identical with the influenza of all other nations.

ANTIQUITY OF INFLUENZA.

Very varying answers have been and probably will be given to the question how far back influenza can be traced by different medical historians. We cannot be surprised at this when we observe the indefinite and fragmentary character of the older reports, recorded very often by a single person, and he not a physician. Some historians of repute believe that the epidemic of the year 412 B. C., mentioned by Hippocrates and Livy, was influenza. Others associate certain portions of Thucydides, excepting, of course, the Attic pest, with influenza. It is obviously impossible to interpret as influenza outbreaks the Sicilian infectious camp diseases described by Diodorus, from the mere fact of the terrible devastations caused by these diseases. We pass over also a similar interpretation of the epidemics of the sixth to the tenth century, which were characterized by cough and other catarrhal phenomena, although in these instances of cough epidemics, the Italian fever, there is more likelihood that the disease may have been influenza. A. Hirsch thinks to recognize the first authentic influenza epidemic in the scanty reports of the year 1173 from Italy and France. Zerviani believes the first epidemic occurred in 1239. According to Gluge, the history of the disease dates from the year 1323. More complete accounts exist of the epidemic of 1387, which Schmeich, Haeser, Biermer, Ruhemann, and Gratz describe as the first true influenza epidemic. Thompson, Zülzer, and O. Seifert are still more cautious, and consider the pandemic of 1510 to have been the first outbreak of influenza.

RETROSPECTION OF THE GREAT EPIDEMICS AND THEIR DISTRIBUTION.

It is not the object of this work to present a detailed history of influenza. We refer the reader seeking for such information to the above-mentioned historians. Only the most noteworthy outbreaks will be mentioned. They occurred during the following eras:

1510: Wide distribution over Europe. Direction in general from south to north. Malta, Sicily, Spain, Portugal, Italy, France, Germany, Holland, England, and Hungary.

1557: The statements as to course and direction are contradictory: Asia, Constantinople, Sicily, then toward the north—Italy, Switzerland, France, Spain, Holland.

1580: First real pandemic: at first a general distribution over the Orient, then Constantinople and North Africa. In Europe the direction in general was from east to west and from south to north. From Constantinople to Venice, Sicily, Italy, France, Spain, Portugal, Hungary, Bohemia, Germany, Holland, Belgium, England, Denmark, Sweden, and Livonia.

Seventeenth century: Very scanty reports concerning influenza. In the year 1627 a great epidemic occurred in North America which was believed to have spread from there to South America (Chile) and thence to the West Indies.

1709–12: Probably a single period of epidemics of wide distribution—throughout Italy, France (1712), Germany, Belgium, Denmark, without particular direction.

1729–33: First invasion, beginning in 1729, with the direction from east to west: Russia, Sweden, Poland, Germany, Austria-Hungary, England, Switzerland, France, Italy, Iceland, and perhaps America also. Second invasion in 1732, presumably beginning in Russia; the direction of the epidemic definitely determined; Poland, Germany, Switzerland, France, England, Italy, Spain, and America (?). Minor outbreaks up to the years 1735–38.

1742–43: Beginning, it would appear, upon the coasts of the Baltic Sea, thence spreading to Germany, Switzerland, Italy, France, Netherlands, England. Minor outbreaks until 1745 (Germany).

1757–58, 1761–62, and 1767: Probably a single period of epidemics which arose first in North America, and thence seemed to have affected the old world; or they may have appeared simultaneously in both hemispheres. Confused geographic picture.

1781–82: Decided pandemic. First appearance in the fall of 1781 in China and India (?); then in December; in Siberia and Russia; in February, 1782; in Finland, then Germany, Denmark, Sweden, England, Scotland, Netherlands, France, Italy, and Spain.

1788–90: A most pronounced pandemic period. Began 1788 in Russia, then Germany, Austria-Hungary, Denmark, England, France, and Italy.

1799–1803: A long period, consisting of several invasions and outbreaks of the disease. The first pandemic invasion began December, 1799, in Russia; then Galicia, Poland, Germany, France, and Denmark. After an interval of five months (analogous to our most recent pandemic), next in October, 1800; furthermore, in the winter of 1802–03, individual local epidemics of considerable territorial extent in France, Germany, England, Switzerland. Minor outbreaks extended up to the years 1805 and 1808. In the years 1811, 1815–16, 1824–26, numerous influenza epidemics occurred in North and some also in South America.

1827: Extensive epidemic distribution throughout eastern Russia, especially in Siberia.

1830–33: This remarkably intense and extensive influenza period, distributed over the entire world, consists of two or three pandemic outbreaks. The first invasion (1830–31) seems to have had its origin in China, affecting in its course Manila, Polynesia, Borneo, Java, Sumatra, and India. The European invasion began, so far as we know, in Russia (October, 1830), extending thence in 1831 through Courland and Livonia, Poland, eastern Prussia, Silesia, and the remainder of Germany, Austria, Finland, Denmark, Belgium, France, Sweden, England, Scotland, Switzerland, Italy. It reached Spain in January of 1832, and at the same time North America. After a pause of one year Europe was infected anew by a second exceptionally intense outbreak, which traveled in the same direction, namely, from east to west. The course of the disease which originated in Russia (January, 1833) is almost identical with the epidemic of 1831–32 just described. Three years later a new pandemic invasion traveled right around the earth.

1836–37: After influenza had raged in Australia, South Africa, Java, and Farther India in the late fall of 1836, there followed the great European outbreak, taking the direction from east to west. It began in Russia in the year 1836, and extended thence in rapid strides to Sweden, Denmark, Germany, England, France, Holland, Belgium, Switzerland, upper Italy, Spain, and Portugal. We can plainly distinguish a primary northern outbreak extending from east to west, and a subsidiary outbreak from this point, with the direction from north to south. The smaller epidemic outbreaks during the succeeding year should probably be considered as sequels of the epidemic of 1836–37.

1847–48: A well-defined direction cannot be determined in this pandemic. After an epidemic had occurred in England, Denmark, Belgium, Switzerland, and France in the years 1846–47, there followed in March, 1847, an outbreak in Russia. But the principal outbreak occurred in September, 1847, first apparently in France, and from there in rapid succession in Germany, Denmark, England, Scotland, Switzerland, Italy, Spain, and Greece. In January, 1848, we find North America affected. Of non-European countries to be recorded are the West Indies, Newfoundland, New Zealand, the Sandwich Islands, Egypt, Algeria, Syria, and the west coast of Africa. The epidemics occurring in the years 1850–51, 1855, 1857–58, and 1874–75, which were counted by A. Hirsch as real pandemics, we consider should not be placed in this category.

1889–90: This, the most extensive and important of all the pandemic outbreaks, extending as it did over all the world, will be described in detail below.

Besides these chief outbreaks of the pestilence recorded in the preceding paragraphs, there were also numerous more or less extensive epidemics, involving a greater or less area. If we carefully analyze the influenza epochs compiled by historians, and especially the description by A. Hirsch, comprising the years from 1173 to 1875, we shall see that in the last century, which was characterized by increasing facilities for the distribution of news, scarcely a year passed in which the epidemic prevalence of influenza in some part of the world is not recorded. Many of these local and limited epidemics were nothing more than late sequels of the great pandemics, often separated by long intervals, the germs of the disease planted by these epidemics having remained alive for years. We must speak of influenza-epochs and not of influenza-years. Many of the other epidemics described as influenza have very probably nothing in common with "influenza vera." They are epidemics of local "catarrhal fever." Here we come upon an important point which we must treat more in detail.

RELATION OF INFLUENZA VERA TO THE SO-CALLED "CATARRHAL FEVER," VULGO "LA GRIPPE."

Although there can be no doubt of the relationship of the previously mentioned world-pestilences to true influenza, as regards the other outbreaks, to which we have also alluded, the numerous so-called "influenza epidemics," there is considerable doubt.

The designation "la grippe," or "influenza," has been current over all the world for a very long time, and is even applied to "a febrile catarrh" of the respiratory tract which occasionally shows a slight epidemic character. It is common practice to designate as grip a comparatively severe "cold," with implication of the tracheobronchial mucous membrane, particularly if the clinical course is characterized by fever and great prostration, and if the disease affects several members of a household or several families in a locality.

There can hardly be a doubt that the schematic chronology compiled by historians of influenza epidemics is often unreliable. This is due to the almost unavoidable (because of the absence of sufficient data) inclusion of numerous epidemics of "catarrhal fever" and "cold." In this respect J. Seitz was perhaps the greatest offender; in his well-known monograph, "Catarrh and Influenza," he regarded both diseases as identical and worked them up into a common statistical mass.

We cannot go into a critical analysis of the earlier influenza epidemics; but a brief review of the pandemics which immediately preceded the latest one will make sufficiently evident the difficulties mentioned above.

It is by no means certain that the limited local epidemics recorded by Korman in 1870 in Coburg, and by O. Seifert in Würzburg in 1883, were identical with what nowadays we call influenza. In the epidemic recorded by Kasin in Russia from 1856–58 the frequent occurrence of certain complications, such as swelling and abscess formation of the glands of the neck, especially of the parotid, purpura, and scurvy, raises suspicions as to the nature of the disease.

W. Zülzer, in 1886, stated: "Even up to the most recent times, influenza keeps up its great marches; at the time at which I am writing these lines, we in Berlin are in the midst of an epidemic of considerable magnitude, where the sick may be counted by the thousands"; the question naturally arises, Was this the same influenza which, three years later, attacked the entire world, and, when it reached Berlin, appeared to the selfsame physicians as an entirely new disease?

The evidence of the epidemic recorded by R. van den Velden in Strassburg in 1874–75 is decidedly more convincing, not only on account of the frequency with which pneumonia was noted as a complication, but chiefly because simultaneously an epidemic was noted in several districts of France, southern Germany, and the Rhine provinces.

It is very questionable whether the epidemics recorded in 1855 and 1862 in Iceland; 1870 in Philadelphia; 1875 in Scotland by Gairdner; 1870 by Handfield-Jones; 1876 in the Fiji Islands; 1887 in various districts of England; in October, 1889, in Natal; in November in Jamaica and Prince Edward's Island—can be classed as true influenza, even when the frequency of pneumonia, especially in the last two districts mentioned, is taken into consideration. As regards the influenza epidemic which in November and December of 1889 existed among the school-children of Pleshey and Great Waltham, and which affected at least 50 per cent., apart from the fact that the pandemic did not appear there until January 1890, the circumstance that the school-children exclusively were affected, is in itself suspicious. Grave doubts must also be entertained in respect of the universally quoted and celebrated "spring catarrh epidemic," which is generally regarded as influenza, which occurred in St. Kilda, Faroë, and Nikobar Islands, etc.

The collective investigations of the last pandemic contained a number of reports based upon retrospective diagnosis, alleging that in numerous districts in Germany "first cases" were observed and even small epidemics took place in the summer and fall of 1889, several months before the actual outbreak of the pandemic in December.

As the result of my own experience regarding the identity of those outbreaks which arose before 1889 and of the small outbreaks of "catarrhal fever and cough epidemics" which have usually been classed as la grippe or influenza, with the true influenza which we learned to appreciate for the first time in the winter of 1889–90, I am of opinion that they were not the same disease. This last real influenza gave the impression of being an affection entirely different from those diseases which up to that time had been generally designated as la grippe, not alone by its appearance as a pandemic world-pestilence and the sudden development of the disease in the majority of the population, but also by its character as a severe general infectious disease, by its entire clinical course, its various and often dangerous complications and sequelæ.

If the micro-organism discovered by R. Pfeiffer maintains its place as the exclusive cause of true influenza, the diagnosis and history of influenza epidemics will have made a decided advance toward certainty of identification in the future. Even if it be too much to expect every practising physician to make his diagnosis depend upon the finding of the bacillus of influenza, the occurrence of an epidemic will give rise to a number of cases in which the specific bacteria will be isolated, so that any existing epidemic may be recognized with certainty as true influenza.

Should, however, the numerous influenza outbreaks and epidemics which A. Hirsch has tabulated in his historic and exhaustive work prove to be one and the same species of influenza,—a possibility that cannot be simply neglected,—influenza would show itself, in respect to its epidemiologic features, as an exceedingly variable and protean affection. It would be possible, under the conditions mentioned, to give the following epidemiologic definition of influenza:

Influenza is a specific infectious disease and usually arises epidemically, but it is, in fact, endemic over all the world (sporadic cases), although in any particular district or place years and decads may pass before the disease shows any great epidemic development. An epidemic of the disease is demonstrable nearly every year in some part of the world. There occurs then, from time to time, starting in some part or center, or from several places simultaneously, from unknown causes, an enormous increase in virulence of the specific micro-organism, with accompanying increase of contagiousness. These are the periods in which influenza spreads in the form of a mighty epidemic over entire countries, a hemisphere, or the entire earth. Our common endemic "influenza" or "grip," which generally occurs sporadically or as a mild epidemic, belongs to the same species of disease as the world pestilence, influenza. It is, however, less virulent and the specific cause has less vitality.

For the present, until a final decision is arrived at by means of bacteriology, we maintain that *influenza nostras* and *pandemic influenza* are just as distinct diseases as are *cholera nostras* and *Asiatic cholera*. According to this view, we divide the diseases designated as influenza as follows:

1. Into the pandemic *influenza vera*, due to the bacillus of R. Pfeiffer.
2. The endemic-epidemic *influenza vera*, which develops after a pandemic from the residual germs (bacillus of R. Pfeiffer). The duration of this endemic stage of *influenza vera* may last several years in individual districts.
3. The endemic *influenza nostras s. notha*, pseudo-influenza, catarrhal fever, *vulgo* grippe, a disease *sui generis*. The micro-organisms of this disease are as little known at present as are those of *cholera nostras*.

EPIDEMIOLOGY OF PANDEMIC INFLUENZA.

Numerous contradictions in the epidemiologic teachings regarding influenza would have been avoided if the writers had recognized that the pandemics which affect the whole world do not follow the same epidemiologic laws as their sequels, or local endemic-epidemic outbreaks.

The most important characters of pandemic influenza are:

1. The appearance of true pandemics at considerable intervals of time—occasionally several decads apart.
2. The usually demonstrable origin of the pestilence from some particular portion of the world.
3. Rapid spread over countries and hemispheres.
4. Extensive affection of the inhabitants in the locality of outbreak.
5. Rapid disappearance of the disease after an existence of several weeks.
6. Entire independence from wind and weather, from season, climate—in short, from all atmospheric-telluric conditions.
7. Disproportion between enormous morbidity and remarkably small mortality.
8. The uniformity with which all ages and occupations are affected.

A detailed investigation of these characteristics of pandemic influenza relieves us from devoting a special section to the ancient controversy: "Contagium or miasma?" This question finds its own solution in the following description, in which the doctrine of the contagious nature of influenza will be fully confirmed.

ORIGIN OF THE PANDEMIC.

Just like our latest pandemic, numerous earlier ones had their origin upon the Asiatic continent and often in the furthermost parts of Russia, spreading over Europe from east to west. This was the case with the epidemics of 1729, 1732, 1742, 1781, 1788, 1799, 1833, 1889. Moreover, numerous other older epidemics, of which Germany seemed to be the starting-point, were probably brought in from Russia, although the accounts of these epidemics are too scanty to prove this.

Besides the customary northerly course of the disease successively through Asia, Russia, and Europe, which was the case in the majority of the pandemics just mentioned, there is also, in our opinion, a southern course (epidemic of 1510 (?), 1557, 1580), in which the disease was probably carried from Russia or Asia by way of Constantinople to the south of Europe. From this point the spread northward took place; in a similar manner, the northern European course, which gradually extended toward the south, and, as history shows, with remarkable regularity finally reached Italy and Spain. The regular Russian North-European course followed the usual trade route between Russia and the other countries of Europe.

Netter and others have put forward the following hypothesis: "Just as cholera is endemic on the banks of the Ganges, and endemic-epidemic in Indo-China, so influenza has its home in the interior of Asia, and its endemic-epidemic domain in the bordering countries, especially Russia." As a matter of fact, influenza appears to have been epidemic here for some time.

Moreover, history teaches that in former times extensive influenza epidemics occurred, limited to North America alone, and that true pandemics appeared simultaneously in Europe and North America (A. Hirsch). From this it may be assumed that a permanent focus of disease, such as central Asia and Russia form for Europe, likewise exists in North America. The following facts, taken from the most recent pandemic, seem to support this view.

As early as May, 1889, influenza appeared in Athabasca (British North America), and in the summer of 1889 Greenland was affected by an epidemic. Of particular interest, however, is the exhaustive report of the extensive influenza epidemic which arose about the middle or toward the end of December (December 22), 1889, in the immense northwest territory of British North America, in Manitoba, the island of Vancouver, situated near the northwestern coast of America, as well as in the east, in Canada and Quebec. An importation of the disease from New York and Boston, which were attacked on December 17, into those distant lonely regions is not possible in view of the time at which the disease appeared in each locality. That we have here to deal with an independent endemic-epidemic analogous to the one occurring in central Asia in July, 1889, appears also from the report. The invasion and the occurrence of influenza in these extensive territories usually take place simultaneously, even in districts widely separated from each other, between which there is no communication by means of the railroad, such as between Forts MacLeod, Saskatchewan, Prince Albert, and other military posts. Moreover, the scattered Indian colonies and tribes, among whom there is only very slight intercourse, were also attacked simultaneously by the epidemic.

THE GEOGRAPHIC DISTRIBUTION OF THE DISEASE IN REGARD TO TERRITORY AND TIME.

Among all the infectious diseases arising epidemically there is none that can even approach influenza in regard to the extent of its geographic distribution over the earth. It is the world pestilence—

χατ' ἐξοχήν, or, as Huxham (1754) described it, the "Morbus omnium maxime epidemicus."

None of the earlier pandemics were nearly so extensively distributed over the entire world as the pandemic of 1889 to 1890.

The enormous development of traffic, especially in travel (traveling influenza patients, convalescents, perhaps also healthy persons), possibly also in merchandise, is chiefly responsible for this.

We must limit ourselves in describing the course of the latest pandemic around the earth to some few especially important landmarks.

It may be regarded as certain that the pandemic of 1889 had its origin in Asia. The first news of the appearance of the pestilence came from Bucham, in the interior of Turkestan, where Heyfelder, medical officer of that section of the Russian railway, recognized the outbreak of an extraordinarily intense influenza epidemic, in the latter part of May or the beginning of June, 1889.

From Turkestan influenza gradually spread through Russia, at first remarkably slowly, as might be expected where traffic is so small. Thus the disease required four months to spread to eastern Russia and Siberia, and five months to reach St. Petersburg.

From Russia and Finland, and especially from St. Petersburg, where the epidemic began in October and reached its acme between the fifteenth and twenty-fifth of November, the disease spread like an avalanche over the whole of Europe.

All the localities in Europe affected by influenza were densely populated, and, commercially united with each other as they were, formed new foci for the further spread of the disease in every direction.*

Within Europe the course of epidemics forms a network which it is impossible to unravel.

Even in the middle of November, fourteen days after the recognition of the first influenza cases in St. Petersburg, the first authentic cases were observed in Berlin, Danzig, Breslau, and even in central Germany, Cassel, Chemnitz, Leipsic, and Halle. Paris became infected only a few days later than Berlin (November 17 to 20). Immediately afterward, that is, toward the end of November, the disease broke out in Stockholm, Copenhagen, Vienna, Cracow, Lemberg, and in the German cities of Hamburg, Kiel, Stettin, Bremen, Hannover, Cologne, and Stuttgart.

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* The rapidity with which our latest pandemic spread over Germany is shown in the following statistics, which I have compiled from the voluminous tables of P. Friedrich. Of 998 places (towns and villages) spread over the whole of Germany, the first appearance of influenza was noted—

End of October	in 15	places	(?)
Beginning of November	in 12	"	(?)
Middle of November	in 16	"	
End of November	in 62	"	
Beginning of December	in 103	"	
Middle of December	in 450	"	
End of December	in 307	"	
Beginning of January	in 33	"	
	998	districts.	

In the beginning of December Königsberg, Memel, Munich, Würzburg, Weimar, etc., Berne, Geneva, Basel, and Zürich were attacked.

It was not until the second week in December (December 11) that influenza was noted in London, and almost simultaneously it appeared in Brussels; also in Portsmouth, Leith, Hull (imported from Riga), and Inverness (Scotland). In the middle of December it was noted in Hungary and the Balkan States, in Holland, in Innsbruck, and in Venice. In the second half and toward the end of December Italy, Spain and Portugal, Bohemia, Moravia, Siebenbürgen, Scotland, Ireland, Athens, and Constantinople became affected. Christiania became affected on December 29, four weeks later than Stockholm. At the end of December we find the disease in Malta, Corfu, Cyprus, and at the same time at the St. Bernard Hospice, at St. Moritz, and at Gibraltar.

Early in its course the disease traversed the Atlantic Ocean, reaching New York and Boston on December 17, from which points the large cities of North America were affected. Nearly six weeks elapsed while the disease was traveling from New York to Hudson Bay, Lake Winnipeg, and Newfoundland. As early as the beginning of January influenza was observed in Canada in Quebec, Montreal, and Halifax.

From Europe influenza reached the north coast of Africa (Egypt and Algeria) early in January, and simultaneously (toward January 7) the most southern point of that continent, the Cape of Good Hope, where the pestilence was conveyed by a ship infected with influenza (the duration of the voyage from London, which was infected on December 10, being twenty days).

In the beginning of January, that is, at the same time as at the Cape of Good Hope, influenza was noted in Trieste, Dalmatia, Sicily, Corsica, Naples, etc., in Antigua (West Indies), Cape Verde, and Persia (Teheran and Tabriz).

By the middle of January the following places were affected: several islands in the West Indian archipelago, Mexico, Honolulu; the interior of Norway, the inhabitants of the Rigi, the Channel Islands, north of Scotland, and the west of England.

Toward the end of January we find influenza in Central America, also in Hong-Kong (a patient leaving London on December 18 at the acme of the disease arrived in Hong-Kong on January 20). From Hong-Kong Colon Bay (China) was infected early in February, though it appears that in both these places the disease was not able to establish itself, since the real epidemic outbreak was first reported in Hong-Kong about the end of February. The numerous contradictory statements that have been made in reference to time and appearance of the first cases of epidemics are to be explained by the fact that the first cases did not take root. This has been noted especially in cases in which the disease has been carried into harbor and coast districts by ships; but also upon the mainland it sometimes requires repeated introduction before developing.

In the beginning of February the following places were affected: Japan (according to the English marine reports), Ceylon, Buenos Aires, Montevideo, Argentine, Rio de Janeiro, Pernambuco, and Guatemala; by the middle of February, Greenland, Scilly Islands, Sierra Leone, and San Francisco.

By the end of February and beginning of March influenza had spread in numerous districts of Farther India, India, China, and thence to Australia (Sydney, Melbourne), New Zealand, and Borneo. About the same time various mountain districts of England (Rieth, Aysgarth, Rishworth, etc.) were affected. We may further briefly note the following districts. From the middle to the end of March Zanzibar, Togo Country, Kamerun, Bermuda, Basutoland, were affected; in the middle of April Hodeida (Arabia), Natal, Bechuanaland, the Azores, Ecuador and Barbados, etc., were attacked. In May the Gold Coast of Africa; in June, Trinidad; in July, Quilimane upon the Zambesi, Madagascar, North China, Iceland; in August, Jamaica, St. Helena, Mauritius; in September, Réunion, the Falkland Islands; in October, the Shiré plateau in central Africa on the Zambesi. The end of this globe-encircling pandemic appears to have been Abyssinia (Shora), in November, and Gilgit, situated in a distant valley of Hindu Kush, in the highlands of Kashmir, in December, 1890.

An exact report of the geographic distribution of the pandemic of 1889–90 over the earth will be given at the conclusion of this section.

The great rapidity with which pandemic influenza becomes disseminated over countries is remarkable. In this respect there is no other infectious disease comparable with it, and yet this rapidity of spread is not, as some have thought, any faster than our speediest methods of communication, the railroad and the ocean steamship.

As in earlier epidemics, so also now, although we are better informed as to the nature of infectious diseases, we have been astounded by the rapidity with which influenza spread itself from Russia over the whole of Europe, and the suddenness and extent of the outbreak among the populace. Impressed by these remarkable features of the disease, at the outbreak of the epidemic of 1889 prominent physicians discarded the opinion that influenza spread by contagion, and accepted a miasma as a pathogenic agent which distributed itself through the air over vast territories.

This alone seemed to offer an explanation of the rapidity of distribution and the simultaneous infection of the masses. Influenza appeared as if wafted by the winds: "It suddenly hovered over a district like the shadow of a cloud." M. Colin in 1889 gave his opinion in the Paris Academy as follows: "The grip is independent of any kind of human intercourse; it travels through densely populated districts and uninhabited regions with the same rapidity as light and electricity." Another favorite comparison was that with the Krakatoa eruption (1883). Just as the volcanic dust from this eruption was disseminated throughout the highest altitudes and distributed itself over a large part of the earth, so influenza was supposed to have originated in Russia in an explosive manner, and to have sown its germs in the air over the entire earth. At the present time no one thinks of such comparisons, for the accurate study of the manner of the dissemination of our last pandemic has proved beyond doubt that the rapidity of distribution was nowhere greater than the rapidity of our most speedy means of transportation. But it is on this account that the latest influenza pandemic has traveled with much greater rapidity than any of its predecessors.

This may be seen by a glance at the following table, which is arranged to show the chronology of the epidemic of 1830–31, compiled according to months. For comparison a second column, showing some localities affected in the last pandemic, is added.

	1830–31.	1889–90.
First month	Moscow.	St. Petersburg, Moscow, Courland, Livonia, Finland.
Second month	Russia.	Berlin, Paris, Vienna, Sweden, Denmark.
Third month	St. Petersburg.	London, Holland, Belgium, the Balkan States, North America.
Fourth month	Courland and Livonia.	Cape of Good Hope, Egypt, Honolulu, Mexico, Japan, Hong-Kong.
Fifth month	Warsaw.	San Francisco, Buenos Aires, India, Sierra Leone, Scilly Islands.
Sixth month	East Prussia and Silesia.	Chile, Kamerun, Zanzibar, Basutoland, Tasmania.
Seventh month	Germany, Finland, Denmark, Vienna.	British Bechuanaland, Barbados.
Eighth month	Paris, Belgium, Sweden, England, Scotland.	Gold Coast, Natal.
Ninth month	Switzerland.	Trinidad.
Tenth month	Italy.	Iceland, Madagascar, Shiré plateau, entire China, Sénégal.
Eleventh month	Spain, North America.	Katunga, Kashmir.

MANNER AND RAPIDITY OF SPREAD OF THE PESTILENCE FORMERLY AND NOW.

Remarkably interesting results are revealed by comparing the course of the epidemic of the spring of 1833 through the Prussian garrisons with the corresponding behavior of the pandemic of 1889–90. In the year 1833 the pestilence, conformably with the means of communication at that time, progressed not only very slowly, but also in an accurate geographic direction from east to west. On the other hand, in the pandemic of 1889–90, a geographic course is hardly recognizable. The sequence in which the Prussian garrisons were attacked is no longer determined by their geographic location, but chiefly by their position as trade centers. The progress of the disease in 1833 was as follows:

March 4, Garrison Memel; March 13, Tilsit, Insterburg; March 17, Königsberg; March 23, Gleiwitz; March 25, Posen; April 8, Magdeburg; April 20, Erfurt; May 1, Minden; May 15, Mainz; beginning of June, Cologne, Coblenz, Aix-la-Chapelle; June 10, Luxemburg.

It, therefore, required three months for the epidemic to progress from the garrison at the extreme east to that at the extreme west. In the year 1889–90 the difference in time between the garrisons was at the most five weeks.

But the order of attack was entirely different in 1889–90. From the end of November to December 6: Berlin, Thorn, Kiel, Stettin, Dantzig; December 7 to 10: Breslau, Dresden, Munich, Potsdam, Halle, Mainz, Strassburg (very likely infected from Paris), Spandau; December 11 to 15: Posen (!), Graudenz, Ulm, Cassel, Darmstadt, Magdeburg, Hannover, Minden, Cologne; December 16 to 20: Leipsic, Würzburg, Stuttgart, Giessen, Hamburg, Königsberg (!); December 21 to 31: Neisse, Riesa, Chemnitz, Zittau, Nuremberg, Ratisbon, Mühlhausen i. E., Karlsruhe, Colmar, Coblenz, Bonn, Münster, Wesel, Düsseldorf, Altona, Schleswig, Gumbinnen, and Insterburg (!). In January: Inowrazlaw (!), Glatz (!), Wiblingen, Lindau, Diedenhofen, Stolp.

In commending this compilation to the reader for closer study we would only add that the German garrisons which remained exempt from the disease were almost all in places like Burg, Bojanowo, Samter, Schrimm, Bernstadt, Parchim, and Roffwein, hardly known to the non-military German even by name.

The fact that in some garrisons the military remained exempt from influenza (Liegnitz, Beuthen, Aurich) while the civilians were severely affected is an occurrence which requires separate investigation (compare p. 571). Occasionally, in earlier times, influenza traveled very rapidly. In 1782 it progressed from Leipsic to Amsterdam in eighteen days, being brought by Dutch merchants returning from the Leipsic fair in this short time to their native country.*

The direction and the road that pandemic influenza follows whenever it spreads over countries and hemispheres, as also when it is restricted to a particular locality, province, or district, are exclusively determined by intercommunication.

The main cities, the capital, and the commercial centers are generally affected sooner than the smaller places; the latter again sooner than the villages and lowlands and the distant mountains.

Isolated districts upon the Russian frontier, numerous purely country districts, the Thüringen and the Black Forests, the Bavarian Alps, the Bavarian woods (Cham, Regen), the higher Harz and Vosges districts, etc., were reached by the disease much later than other sections.

The districts situated upon the railroad, as shown by numerous examples, are, as a rule, affected much earlier than those situated at some distance from the railroad.

When influenza is carried by ships, it is the coast and harbor cities of those parts of the world to which the ships are sailing where the disease will enter, and the time of infection of the interior portions of such countries will depend upon the rapidity of travel, as was observed especially in Australia, in Africa upon the Zambesi, in Ceylon, and in many other seaport towns.

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* Bossers, *loc. cit.*, p. 39.

Innumerable examples might be quoted to prove the above-mentioned behavior of influenza, but at the same time there are many and noteworthy exceptions to the rule.

To quote but one example, it appears that Königsberg, which is the entrance port to Russian commerce, was attacked considerably later than Berlin, Paris, and many of the cities in the extreme west of Germany.

Accident plays so large a part in the spread of contagious diseases that occasionally small districts, hamlets, villages, and isolated farms may be affected by influenza sooner than large cities in their immediate neighborhood. Numerous proofs might be adduced to substantiate this. The Bavarian report shows that the large cities of Munich, Nuremberg, Würzburg, Augsburg, and Ratisbon were affected later than the smaller rural places. A simultaneous affection of both city and country is occasionally noted. In densely populated districts the rapidity with which the disease spread in town and country was so great that a difference of date of infection could not be observed. In sparsely populated districts with widely distant villages influenza required more time to spread over a small area than it did to spread over the main cities of Europe and over the ocean.

As an example, the behavior of influenza in the province of Schleswig-Holstein may serve. The capital, Kiel, was one of the first districts in Germany to be affected, and yet influenza required fully two months to spread itself to the more distant and isolated districts of the province.

In the purely rural districts of Salford (England), influenza required a period of four months (December to March) to spread; while in the industrial cities a few weeks were sufficient.

Numerous remarkable exceptions to this rule have been noted in literature also, but we need only allude to the rapid spread of the disease among the almost isolated and widely separated farm-houses in the district of Bradwell—"the strongest piece of evidence of the atmospheric origin," as the author thinks.

Attention must also be drawn to the exceptionally slow spread of the epidemic in England. Is it not remarkable that although London was infected on December 11, cities of the magnitude of Birmingham, Manchester, Glasgow, Sheffield, Liverpool, Edinburgh, and others were first affected toward the end of December or the beginning of January?

In sparsely populated districts, in which the course of the disease could be more accurately observed, it could readily be seen that influenza spread gradually in all directions from the district which was known to have been first affected—that is to say, it radiated from a common center. On the other hand, in districts in which communication was more general, the leaping or vaulting character of the disease was often very marked. One need only remember that in the case of the pestilence which spread from Russia, Paris and

London were affected much earlier than innumerable cities and many provinces of Germany, even than those lying close to the Russian frontier.

These observations settle the old controversy of historians as to whether influenza is invariably distributed in a leaping or in a radiating manner. As a matter of fact, both modes occur according to the manner and means of intercourse.

But few places, in Europe especially, remained unattacked by influenza in 1889 and 1890. They were without exception districts not in ordinary communication with the outside world, such as villages, hamlets, deserts, desolate places, coasts, forest valleys, peaks of hills, and mountains. The following places have been definitely shown to have been exempt: Isle of Man, several West India Islands (Bahamas, Grenada, St. Lucia), the farther British Honduras, British New Guinea, and the Seychelles.

Upon the Säntis (observatory, 2504 meters) every one remained well, "because during the whole time of the epidemic no one descended into or ascended from the valley."

Localities which were temporarily cut off from outside communication were affected by the influenza at correspondingly later dates.

Upon the island of Borkum, which, on account of the frost, was isolated from the mainland from Christmas to the fifth of January, the disease showed itself on the eighth of January, four days after the arrival of the first vessel.

In several localities of the Weser marsh (Kreis Achim), which, on account of flood, was cut off for weeks, the disease arose at a correspondingly later period.

Vladivostok and the island of Sakhalin were not attacked until the spring of 1890, after communication by sea was again established.

If we inquire what are the reasons why influenza, as compared with other contagious diseases, spreads with such rapidity over land and sea and brings about such universal infection, they would appear to be as follows: The marked virulence of the contagion; the ease with which the germs are conveyed from their original seat in the mucous membranes of the respiratory apparatus to outside and all around by coughing, sneezing, and expectoration; the enormous number of slightly affected persons who carry on their vocation and intercourse with their fellowmen, and who travel about to all points of the compass without hindrance; the probable longevity of the germs in convalescents; the brief period of incubation,—one to two days,—on account of which the number of those affected grows to an enormous extent within a few days; the almost equal susceptibility of all people, every age, and vocation; the probable transmission of the germ by healthy individuals and by merchandise of various kinds, and for short distances also through the air. We are conditional supporters of the doctrine regarding the distribution of influenza germs by means of the air.

SPREAD OF THE PANDEMIC OF 1889 AND 1890 AROUND THE WORLD.

June, 1889.
Turkestan.
Beginning of October (1–10).
Wjätka (Eastern Russia).
Middle of October (11–20).
Western Siberia (Tomsk, Perm).
Southeastern Russia (Ufa, Astrakhan).
End of October (21–31).
St. Petersburg, Peterhof, Kronstadt, Gatschina, Ligova, and the province of Kostroma.
Beginning of November (1–10).
Caucasus, Riga, Pskof, Vilna, Kaluga, Moscow, Sevastopol, Tver, Yalta, Murow, Kasimof, Klin.
Middle of November (11–20).
Charcow, Orenburg, Odessa, the Baltic provinces, Finland (Helsingfors, Abo), Berlin, Potsdam, Charlottenburg, Dantsig, Elbing, Breslau, Cassel, Chemnitz, Leipsic, Pirna, Halle, Zwickau.
Paris.
End of November (21–30).
Baku, Caucasus, Vladikavkaz, Hamburg, Kiel, Stettin, Bremen, Hannover, Cologne, Stuttgart, Copenhagen, Gothenburg.
Stockholm.
Vienna, Lemberg, Cracow, Galicia, Neuenburg, Le Locle, Lausanne, Aarau, Zürich, Basel.
Geneva.
Beginning of December (1–10).
Altona, Königsberg, Memel, Frankfort-on-the-Oder, Rostock, Braunschweig, Weimar, Coburg, Munich, Würzburg, Münster in W., Düsseldorf, Essen, Trier, Giessen, Thorn.
Montpelier.
Prague.
St. Gall, Winterthur, Lucerne, Bienne, Coire, Davos, Interlaken.
Middle of December (11–20).
Lübeck, Stralsund, Flensburg, Husum, Lauenburg, Oldenburg, Dresden, Magdeburg, Erfurt, Eisenach, Jena, Gotha, Greiz, Gera, Posen, Arnsberg, Elberfeld, Barmen, Gladbach, Crefeld, Aix-la-Chapelle, Bonn, Coblenz, Bielefeld, Bochum, Dortmund, Hamm, Osnabrück, Detmold, Frankfort-on-the-Main, Hanau, Marburg, Wetzlar, Kreuznach, Heidelberg, Karlsruhe, Darmstadt, Mainz, Worms, Nuremberg, Erlangen, Aschaffenburg, Kempten, Ulm, Augsburg, Passau, Ratisbon, Rosenheim, Reichenhall, Speyer, Lindau, Esslingen, Heilbronn, Tübingen, Strasburg, Metz.
Lille, Brest, Valenciennes, St. Omer, Arras, Lyon, Marseilles, Toulouse, Bordeaux, Besançon, Roubaix, Rouen.
Budapest, Trieste, Innsbruck, Linz.
London, Oxford, Portsmouth, Hull, Leith, Inverness, Winchester.
Brussels, Antwerp, Specia, Venice, Piacenza, Monaco.

Einsiedeln, Schwyz, Olten, Zug.
Madrid, Barcelona, Malaga, Lisbon, Oporto.
New York and Boston.

End of December (21–31).

Merv, Ashkabad, Transcaspian province.
Christiania.
Wiesbaden, Lüneburg, Bocholt, Paderborn, Fulda, Neuwied, Berchtesgaden, Kelheim, Kaiserslautern, Dürkheim, Cham, Kronach, Eichstätt, Kitzingen, Bingen, Immenstadt, Kaufbeuren, Horb, Saalfeld, Oppenheim, Edenkoben, Baknang, Nagold, St. Blasien, Eberstadt, Offenbach.
Douai, Dunkirk, Aire, Calais, St. Denis, Saument, Nimes, Toulon, Belfort, Havre, Montbéliard, Dieppe, Marseilles, Toulouse.
Brünn, Hermannstadt, Bozen, Meran, Graz, Klausenburg, southern Hungary.
Birmingham, Bristol, Liverpool, Dover, Edinburgh, Canterbury, Aberdeen, Dublin, Cork.
Dordrecht, Delft, Leeuwarden, Breda, Amsterdam.
Rome, Turin, Milan, Bologna, Messina, Catania, San Bartolommeo, Port Usola, Genoa, Gaeta, Naples.
St. Moritz, St. Bernard, Lugano, Locarno, Bellinzona.
Gibraltar, Valencia, Saragossa.
Bukharest, Sophia, Belgrade, Rustchuk, Tirnova, Montenegro, Galatz, Braila, Athens, Constantinople, Corfu, Cyprus, Malta, and the Ionian islands.
Rochester, Philadelphia, Baltimore, Chicago, Canada, Halifax, Quebec, Montreal, Toronto, Buffalo, Kansas, Detroit, Bath, Brockton, Massachusetts, Clinton, Prince Edward Island, and Ontario.

Beginning of January (1–10).

Liebenwerda, Prettin, Burghausen, Münsingen, Butzbach, and other small places.
Boulogne, Condé, Arles.
Manchester, Glasgow, Sheffield, Dinswall, Belfast, Galway.
Dalmatia (Zara, Fiume), upper Styria.
Antigua (West Indies).
Palermo, Modena, Corsica.
Cairo, Alexandria, Morocco, Algiers, Tunis, Tripoli.
Cape of Good Hope, Cape Verde (St. Vincent).
Persia (Teheran).

Middle of January (11–20).

The interior of Norway.
Crail, Caithness, Southerland, Wick, Channel Islands (Jersey, Alderney), western England.
The Rigi.
Scheveningen.
Madeira.
Honolulu.

End of January (21–31).

Mexico, Guatemala, and Tobago.
Hong-Kong, Colon Bay.
Japan.

Beginning of February (1–10).

North and northwest of England, Cheshire, Lancaster, Cumberland.

Buenos Aires, Montevideo, Santos, Rio de Janeiro, Pernambuco.
Hudson Bay, Saskatchewan, Lake Winnipeg, Newfoundland, St. Kitts.
Nevis (West Indies).
Colombo (Ceylon).
    Middle of February (11–20).
Scilly Islands (England), Lancashire, the Hebrides.
Greenland, San Francisco (?).
Havana.
Sierra Leone (Freetown), Gambia.
    End of February (21–28).
Lucknow (India), Bombay.
Hong-Kong, Singapore, Delhi.
Acapulco (Mexico).
    Beginning March (1–10).
Moreton Hampstead, Rishworth, Reeth, Aysgarth, and the hilly districts of England.
Paona, Benares, Meerut, Penang, Borneo.
Victoria, Sydney, Melbourne, New Zealand.
Chile, Peru.
Sultanabad (Persia).
    Middle of March (11–20).
Lisbon and Portugal (second epidemic).
Calcutta, Madras, Wellesley.
    End of March (21–31).
Bermudas.
Zanzibar, Togo Country, Kamerun, Basutoland.
Tasmania, Kingstone, in South Australia.
    Beginning of April (1–10).
Callao (Peru).
Azores.
Hodeida (Arabia).
Gold coast, Natal.
Burma (India).
Tientsin (China), Malacca.
    Middle of April (11–20).
Ecuador (Guayaquil, Quito), Barbados, Queensland (Australia).
British Bechuanaland.
Mauritius (Africa).
    Beginning of May (1–10).
Mandalay, Farther India.
    End of May (21–31).
Different parts of Natal.
    June.
Trinidad (West Indies).
    July.
Senegambia, Rodriguez, Madagascar, Quilimane on the Zambesi.
The whole of China (Peking) and Iceland.
    August.
Jamaica, Katunga (Shiré Highland, Central Africa), Japan (second epidemic).
    September.
Falkland Islands, Réunion (Africa), Tokio, Yokohama.

October.
Shanghai, Yun-nan (north China).
November.
Abyssinia (Schoa).
December.
Gilgit in Kashmir upon the Hindu Kush.

BEGINNING, ACME, AND END OF THE EPIDEMIC.

There is no infectious disease which, wherever it breaks out, in so short a time causes such universal infection as influenza. This epidemiologic peculiarity of the pestilence produces an enormous disturbance in trade and traffic, which was well seen everywhere in various degrees during our last pandemic, and of which striking examples are recorded by the historians of earlier epidemics.

There is no doubt that the "suddenness of the universal infection" which furnished the chief reason for believing in the miasmatic nature of the contagion, has been greatly exaggerated. Gradually proofs accumulated, especially from the smaller, more easily supervised cities, that isolated cases, gradually increasing in number, were the precursors of the actual epidemic. The first implanted seeds were frequently overlooked, considered as simple coryza or catarrhal fever, and only retrospectively diagnosed and classified after the outbreak of the pestilence.

The following rules are deduced from the enormous amount of material in reference to the beginning, acme, and end of the epidemic, collected from the innumerable localities affected in Germany, England, Sweden, and Switzerland (Parsons, P. Friedrich, Rahts, Linroth, H. Schmidt). We are considering pandemic influenza only.

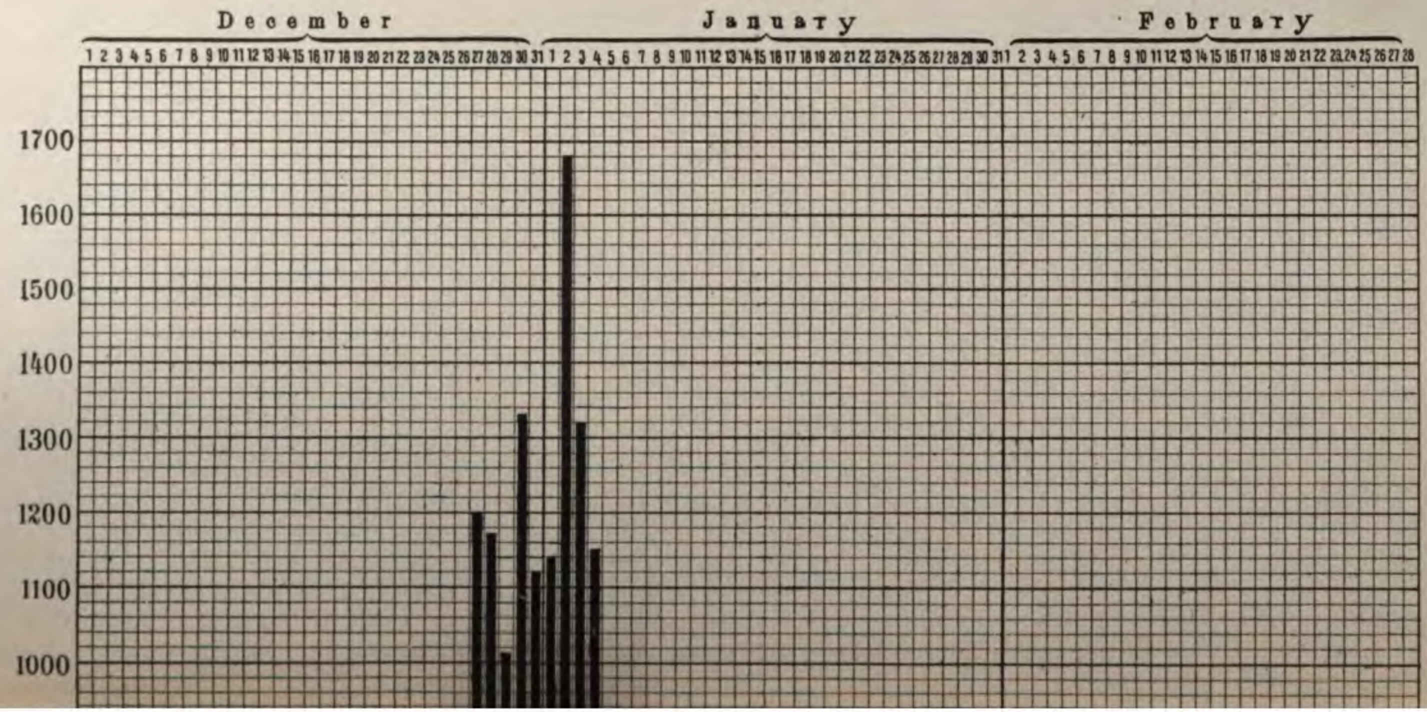
From the date of the first cases until the time of the epidemic frequency—we call this the period of invasion—an average of fourteen days elapses. From this time onward the epidemic develops rapidly, attaining its acme in fourteen days, or at the longest in three weeks, and then comes, as a rule, quickly to an end in a further period of fourteen days to three weeks.

It follows, therefore, that the duration of the actual epidemic period is from four to six weeks, and if we add to this the period of invasion, a total duration of the epidemic of from six to eight weeks.

After the epidemic follow the "trailers," in gradually diminishing number.

An excellent example of this behavior is found in the influenza epidemic of 1889 and 1890 in Munich, in which place, of all German cities, the most exact morbidity statistics were kept (by the adoption of com-

PLATE VIII.


December
January
February
1700
1600
1500
1400
1300
1200
1100
1000

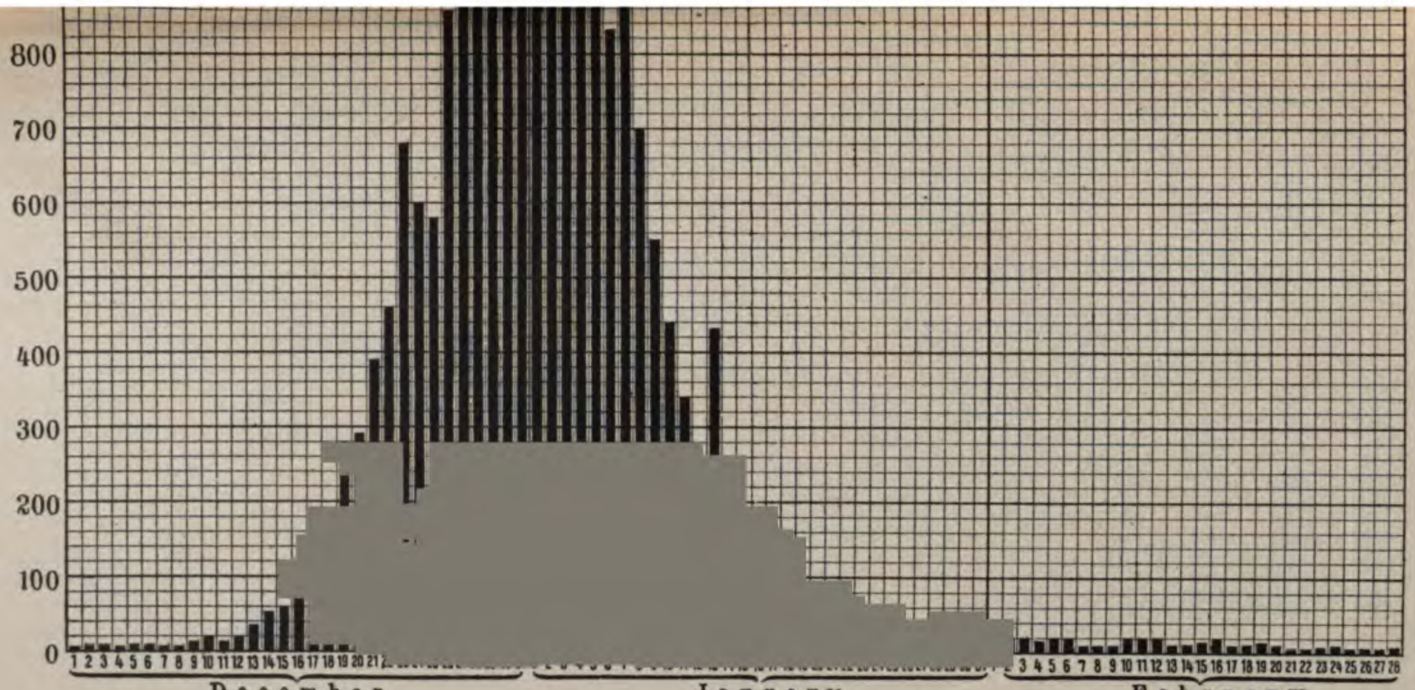


Chart showing the daily report of influenza cases in Munich during the months of December, January, and February, 1889–90.

pulsory notification). We would refer our readers to the graphic representation of the periodic course of this epidemic on Plate VIII., which faces this page. It is taken from the treatise of P. Friedrich. Similar instructive curves are found in the articles by Leichtenstern, Parsons, and Ripperger.

All the earlier pandemics, so far as is known, followed the abovementioned law. This was verified in 1889 in all countries outside of Europe; thus the duration of the epidemic of Massachusetts (Abbott's Collective Investigation) was seven weeks; in Australia, eight weeks; in St. Johns (Newfoundland), six weeks, etc.

The reasons for this regular behavior on the part of the pandemic will be found below. Here it need only be emphasized that the sudden disappearance of the pandemic is only a natural consequence of the rapid universal infection, which in a short time produces immunity among the inhabitants. We must also take into account the fact that the germs, after they have passed through innumerable generations, lose a great part of their virulence and contagiousness.

EPIDEMICS FOLLOWING THE PANDEMIC.

In the earlier influenza epidemics we know that, as a rule, after intervals of several months or longer, epidemic outbreaks of more or less extensive geographic distribution follow the first great pestilence.

Obviously, therefore, the epidemic of 1729–1730 has some relation to the outbreak of the pestilence in 1732 and 1733. The great pandemic of 1782 most likely had genetic forerunners in the years 1780 and 1781. The epidemic of 1788 continued with intervals to the year 1800, and perhaps stands in direct connection with the epidemics of 1802, 1803, 1805, and 1806.

Of especial interest is the pandemic pestilence of 1830, which continued into the years 1831 and 1832. In 1833 a second pandemic invasion occurred again, starting from Russia. The epidemic of the years 1836 and 1837 had trailers until 1838 and 1841. The epidemic of 1847 and 1848 recurred at intervals until the year 1851. History teaches us then that influenza periods often last for several years, and have frequently long intervals of time between the separate endemic-epidemic portions.

After the disappearance of our latest pandemic many thought, without reflecting upon the lessons of history, that the epidemic form of the disease would slumber once more for decads until a new pandemic analogous to the one through which they had just passed should attract the attention of later generations.

The cases of influenza which everywhere arose sporadically in the course of the year 1890 remained isolated, or at the most formed a small epidemic. Only in a few districts of Europe (*i. e.*, Lisbon, Nuremberg, Paris, Copenhagen, Edinburgh, Riga, London, Fünfkirchen, and Detmold) did a few recurrent epidemics take place in the year 1890; but in Japan only, in August, 1890, was there a marked recurrence. These are easily explained as arising from the residual germs of the pandemic.

Only one year after the end of the great epidemic influenza reappeared. In January and February, 1891, there were marked epidemic outbreaks in Buenos Aires and Chile, but particularly in North America (New Orleans, Chicago, Washington, Boston, San Francisco, etc.), and simultaneously in the north of England (Durham, North Yorkshire, Abertillery, etc.). In both countries a further distribution of the pestilence took place during the months of March and April, New York being affected in the third week of March and London not until the beginning of May. In May, too, there were epidemics in Sweden and Norway, and in Denmark during June.

But all other European countries, notably Germany and France, which were especially exposed to the introduction of influenza from America and England, were entirely exempt.

In spite of these facts the simultaneous North American and English epidemics were considered by some to be one and the same, but also to have given rise, as centers of infection, to the entirely isolated local epidemics which arose during April in Portugal, southern Russia, and Poland; in June, in Egypt; in August, in St. Petersburg, which they regarded as terminal trailers of the Anglo-American epidemic. All these opinions are purely imaginary products and lack any foundation in fact. Parsons already rejected the idea that the English spring epidemic of 1891 arose from the coexisting American one. In this he was justified, for a glance at the mode of distribution in England shows that influenza first occurred upon the northeastern coast, in rural districts and cities of the interior which had no direct means of communication with North America. Even assuming that the pestilence was imported from America to England, why was it not also brought to Germany, Holland, Belgium, and France? Not one instance can be found of the introduction of the disease from highly infected England into Germany, not even during May, the principal month of travel, at which time the epidemic had reached its acme in in London.

A. Netter describes the character of these successive epidemics with the words, "The grippe occurred in simultaneous or successive outbreaks, and one could not classify in any manner the various foci, as had been possible during 1889–1890. Very likely there were recurrent outbreaks of the epidemic at various places."

Shipping also, which in the pandemic of 1889–1890 played so very important a rôle in the dissemination of the pest over the earth, proved, in the spring of 1891, to be absolutely without influence in spite of the fact that the chief maritime country, England, was then the hotbed of influenza. In order to explain this immunity of the European continent refuge was taken in the expression "alternating national immunity." Because England had escaped so easily (?) in 1889–1890, she was less immune to the germs introduced from America in the spring of 1891.

Is it probable that the German, French, and other nations at that time were more immune than the Americans and English?

In this first epidemic reappearance of influenza after the pandemic we find the epidemiologic character of the disease markedly altered, and this change in character becomes more striking if we glance for a short time at the later epidemics.

The third tremendous epidemic dissemination of influenza, a true pandemic, began in the fall (October) of 1891 and continued during the entire winter, up to the spring of 1892. It prevailed most extensively over the whole of Europe and North America, but was also noticed during this period in all other parts of the world: in Africa (Egypt, Sierra Leone), in the Azores, Samoa, in Havana, in Persia, China, Japan, in Australia (Melbourne, Sydney), etc.

The following are briefly the most important peculiarities of the two epidemics of the spring of 1891 and the great winter epidemic of 1891–1892. The geographic manner of distribution no longer conforms to any rule—the origin is not from a single center (as in Russia in 1889); there is no continuous progress along trade routes. The law observed in the pandemic, that the large cities and commercial centers are attacked earlier than the open country and places situated on the principal highways (railroads, harbors) earlier than isolated or inland towns, does not hold good in the later epidemics.

In England the spring epidemic of 1891 began in numerous rural districts. For nearly four months the disease raged in the north before it reached London, about the beginning of May (!). A similar condition of affairs occurred in Australia.

In these epidemics there is no definite direction of spread. They can only be limited chronologically, not geographically. The attempt to construct pestilence routes has proved to be completely illusory. In various parts of countries epidemics arise simultaneously, last a longer or shorter period, and then recur after a brief pause. In the interior of large countries, which on the whole remain free from the epidemic, isolated local epidemics of some degree of magnitude and duration may occur; whereas the immediate neighborhood may remain entirely free or become affected only at some later period.

Commerce, as a whole, no longer plays an appreciable rôle. Importation of the disease hardly occurs. We must not, however, overlook the fact that the densely populous and commercially most active civilized countries, namely, Europe and North America, form the principal points of selection of later epidemics; and that in some small districts the spread of the disease can occasionally be shown to be in accordance with the conditions of traffic—*e. g.*, in Mecklenberg-Schwerin. Note must also be taken of the fact that at this time, as in the actual pandemic, the north of Germany was obviously affected some time before the southern German states.*

The Würtemberg report of the epidemic of 1891–1892 says: "The capital and several of the neighboring cities were affected only to a slight extent by the epidemic. In some few districts several isolated portions and villages were very severely attacked; the remainder, on the contrary, were hardly affected at all."

Wutzdorff remarks, in summing up: "One of the peculiarities of the epidemic in question (1891–1892) was that in the neighborhood of markedly affected districts some distinct localities were quite exempt or only affected to a very slight degree." Further: "Some observers who noted the first appearances of the disease in distant isolated localities believed that during this epidemic (1891–1892) human intercourse played a very much less important rôle in the spread of the disease than it did in the pandemic of 1889–1890."

In almost every case, at the point of its origin, the epidemic developed and spread slowly, and only after several weeks did it reach its acme, dying out as gradually as it arose. In almost every case, especially in that of the winter of 1891–1892, the duration of the epidemic was from four to five months; and occasionally it showed exacerbations and remissions. The morbidity, in spite of the long duration, was markedly less. All this forms a striking contrast to the explosive commencement of the pandemic of 1889, when the acme was reached after fourteen days and the duration was strictly limited to six to eight weeks.

The rapid spread of the disease in any area, so characteristic of the pandemic, was never even approached in any of the later epidemics. The spread, even in small districts, as, for example, in a Prussian province, often required several months more time than the pandemic in its cyclonic spread over the entire world.

From the statistical summary of Wutzdorff we see that the epidemic of 1891–1892 in all German cities required several months, usually from October or November to February or March. In Danzig it took from October until May; in Breslau and Liegnitz, from September until April.

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* Compare Wutzdorff, "Arbeiten aus dem kaiserl. Gesundheitsamt," vol. ix, with tables.

Much the same happened in England, Denmark, France, and Sweden. The spring epidemic of 1891 in London lasted from April to July; in Copenhagen, from May until August. The winter epidemic of 1891–1892 in London lasted from December to April; in Edinburgh, from November until February; in Paris, from October until January; and for the same space of time in St. Petersburg, Vienna, etc.

Isolated exceptions were noted, however, to the rule just quoted. In Yorkshire (Weath on the Dearne) the epidemic suddenly arose between the eleventh and thirteenth of April, 1891, reached its acme in ten days, and in twenty days more rapidly disappeared. Similar exceptional outbreaks occurred in Sheffield, where the first pandemic arose in a slow and fluctuating manner and declined gradually, whereas the second epidemic of 1891 arose like an explosion, being of brief duration and rapid disappearance, but showing a considerably greater mortality than in 1889 (339 deaths in 1891 as against only 96 in the pandemic).

In general the lessened morbidity and the less explosive character of influenza in the later epidemics appear also from the fact that there was only occasionally any necessity for closing the schools, as Wutzdorff shows in his official report. In the same way the rapid overfilling of the hospitals with influenza patients, which took place in 1889–1890, did not occur. Moreover, there was not the same sudden attacking of the masses, particularly of the officials of railroads, postal and telegraph bureaus, the employees of large warehouses, factories, offices, theaters, the officials of the courts, etc., as in the pandemic of 1889–1890, where official functions, trade, and commerce were brought to a standstill. Another peculiarity of the later epidemic may be found in the more dangerous character of the disease, as is shown especially in the English statistics, with the decidedly greater mortality.*

The clinical picture of the disease, with its numerous complications, remains the same, unaffected by the change of epidemiologic character.

The epidemiologic facts just mentioned—(1) The generally diminished morbidity of the later epidemics; (2) the diminished geographic distribution of the disease and the scarcely recognizable character of its communicability; (3) the slow development and extension over several months, shown by the later epidemics; and (4) the continuous diminution in frequency and intensity of epidemics from

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* See section on Mortality.

1889 up to this time—may be explained by a successive lessening of the susceptibility of the population, due to their immunization from the preceding attacks of the disease.

But we must be careful not to wish to prove too much with this "immunity of the population." New York, Copenhagen, London, and numerous places in England (see Parsons' report) were severely affected each time, with very marked morbidity (see section on Immunity and Morbidity), in each of the three successive principal epidemics.

The immunity acquired after an attack of influenza unquestionably plays an important epidemiologic part. But, in addition, another important explanatory factor exists, namely, the gradually increasing diminution of the *vis contagii*, that is, of the "virulence of the contagious material from epidemic to epidemic."

Wutzdorff thinks that the supposition of the lessened virulence of the later epidemics is not consistent with their notoriously greater malignancy (mortality). We cannot admit this.

A germ may become less virulent in the sense of being less contagious, but may become more virulent in the sense of being more pathogenic, especially in the case of the dangerous "mixed infections." At the beginning of the pandemic of 1889 the *vis contagii* was, as is well known, enormous; the *vis morbi*, on the other hand, was so slight that it gave rise to ludicrous names ("influenza dinners"). In the later epidemics the *vis morbi* became more pronounced with the decrease in the *vis contagii*, owing, perhaps, to the weakened influenza germs entering into closer symbiosis with other pathogenic microbes.

But the increasing immunity of the population and the decreasing virulence of the germ do not easily explain in a satisfactory manner the above-mentioned facts and many others which occurred in the study of the peculiarities of the after-epidemics. To illustrate this we will take one example, namely, the interesting and important question of the cause of the lessened communicability of the disease in later epidemics.

As before mentioned, the most striking instance is seen in the entire immunity of the greater part of the European Continent in the spring of 1891, at the time of the great North American and English epidemic. If we inquire closely into this epidemic, we see that in the countries affected by the disease communication still played a slight rôle in the transmission of the pestilence.

In the descriptions all the well-known phenomena of the first pandemic are seen again. The infection from person to person, the importation of influenza by one affected with the disease into an immune family, into a house, an insane asylum, a village, etc., all occur. But the numbers of these examples are infinitesimally small when compared with the innumerable ones caused by the pandemic. Viewed alone, influenza still appears to be as contagious as it was at the time of the pandemic. Why should not the disease be disseminated in all directions, as it was then?

We have already mentioned the slight morbidity of the postpandemic epidemics. The danger of importing the contagion from *a* to *b* is proportional to the number of sick in *a* and the susceptibility to infection of persons in *b*. If, for example, in the first pandemic 50 influenza patients from *a*, all infected with germs having their full virulence, had arrived in a large city, *b*, which was highly susceptible, contagion and a further spread of the disease would have followed rapidly. If, on the contrary, in the spring of 1891, on account of the lessened morbidity, there were in *a* only ten influenza patients, only a part of whom were infected with germs of full virulence had arrived in *b*, which in the mean time had acquired immunity, it is probable that the disease would have spread but very little. In this way we can explain the exemption of Germany and France in the spring of 1891 at the time of the North American-English epidemic.

Through the considerably severer character of the disease in the after-epidemics the number of slightly affected persons able to travel was less, with consequent decreased transportation of the disease. Moreover, the fear of influenza in general was greater, so that the patients with but a mild attack took better care of themselves and remained at home. Nevertheless, the epidemiologic character of the after-epidemics must be designated as peculiar. A completely satisfactory explanation is not forthcoming even to-day.

The tangled knot becomes looser, without, however, becoming disentangled, if we glance over the disconnected geographic picture of the after-epidemics. A detailed study of them reveals the following facts:

The epidemics which followed the primary pandemic arose from the germs which remained. They are, for the most part, autochthonous, local or endemic epidemics, which are but rarely genetic; that is to say, caused by the transmission of the germ successively from place to place. Contagion takes place from person to person to a slight degree, and it may even be carried from place to place; but, as a whole, influenza no longer follows trade routes. The rôle which communication played in the pandemic is taken in the after-epidemics by time and location (that is, the place where living germs have remained. We by no means incline to a "contagious-miasmatic" or "locality" hypothesis, which, in the light of our present knowledge, would be ridiculous. But even confirmed contagionists, when explaining the trailing epidemics, are right in using the expression, "the residual germs," although they do not give the reason why these germs remained. We will not discuss this question. Those contagionists who deny a protracted existence of the influenza germ in the external world, because the bacillus is extremely sensitive to drying and all other external influences, and because no permanent form is as yet known, believe that the germ continues to thrive in an attenuated form in the nasopharynx of individual patients. But the reasons why development of these endanthropic attenuated germs should suddenly become virulent again and cause a local epidemic, are as little known to the extreme as to the moderate contagionists, who consider it possible that the influenza germs may lie dormant outside of the human body in a permanent form which is as yet unknown.

Since R. Pfeiffer and Kruse have seen the influenza bacilli thrive for months in the sputum of tuberculous subjects who were affected by influenza, Bäumler thinks it possible that patients afflicted with chronic diseases of the chest, who often travel much, can very easily disseminate influenza. We cannot attribute any epidemiologic significance to this assumption.

After the great pandemic influenza became an endemic disease in innumerable areas of the earth, and especially in the whole of Europe and of North America, and then showed the same fluctuating epidemiologic character, the same puzzling behavior, so far as the time and place of the epidemics were concerned, as other endemic contagious diseases, like scarlet fever, measles, diphtheria, epidemic cerebrospinal meningitis, and others.

This conception of influenza is in harmony with the fact, which has been almost unnoticed up to the present time, that the true endemic influenza, in contradistinction to the pandemic one, is markedly seasonal. Not only the spring epidemic of 1891 and the winter epidemic of 1891–1892, but also the more important epidemic outbreaks of the following years, up to the present day, generally appear in the fall, winter, and spring months, while summer represents the dormant period. We would here call attention to the fact that influenza shows the influence of season (compare p. 533) at the elective point of origin of the great pandemics (central Asia), where, in the fullest sense of the term, the disease is endemic. Almost all the pandemics of this and the previous centuries have started from Russia in the fall, winter, and spring months. Such was the case in the pandemics of 1729, 1782, 1788, 1789, 1799, 1805, 1830, 1833, 1836, and 1889.

We can now recognize also the reasons why the older authors, from Most to Zülzer, were so at variance regarding the influence of season, the laws which govern the areas involved, and the time consumed in the dissemination of influenza. Naturally those younger authors also, who, immediately after the latest pandemic, tried to apply their experiences to influenza as an entity, were led into the same contradictory statement.

We know that influenza presents at least two phases, one pandemic and the other endemic, and they follow different epidemiologic rules.

Even if, as we have shown above, the origin of the later epidemics depended chiefly upon season or location (that is, places where germs capable of further development have remained), this fact, nevertheless, does not in the least affect the "contagious" theory. All the cases of influenza which followed the primary pandemic of 1889–1890, both the continued sporadic cases as well as the occasional local epidemics, were derived from the germs that had been disseminated over the whole earth by the pandemic, and which always and everywhere have multiplied in an exclusively endogenous (endanthropic) manner, and have been distributed by contagion. But we can no more answer the question why, after the cessation of the pandemic, the germs which had everywhere been left behind and had continued to be propagated for months by sporadic cases with lessened virulence (a relative latent period), should suddenly produce marked local epidemics of increased virulence and contagiousness, than we can say why scarlet fever, measles, diphtheria, and epidemic cerebrospinal meningitis should show a similar changeable epidemiologic character. Parsons' statement, that "A periodic multiplication and an increasing virulence, with a converse diminution in these phenomena, is an established biologic law in the life of pathogenic micro-organisms," is only a paraphrase and not an explanation.

In view of the fact that the intensity and frequency of influenza epidemics have universally diminished from year to year since the last great trailing epidemic in the winter of 1891–1892, and that the recent winters have gone by without any outbreaks worth mentioning, we may hope that the present septennial influenza period is nearing its termination. The germs that were distributed by the pandemic of 1889–1890 will gradually die, and the influenza vera disappear. It is to be hoped that many decads will pass before a new powerful pandemic will distribute the germs over the earth and render them virulent for years.

As we have considered in the preceding sections the epidemiology of influenza on a large scale, we will now view it in detail—that is, in families, inclosed institutions, in high altitudes, and upon the seas. Following this we shall discuss the important etiologic and epidemiologic factors, such as immunity, period of incubation, morbidity and mortality, the influence of age, meteorologic conditions, etc.

INFLUENZA IN FAMILIES, HIGH ALTITUDES, AND AT SEA.

The numerous instances recorded in literature regarding the direct transmission of influenza from person to person can be only partially substantiated. In many cases other explanations are possible. With an infectivity like that of influenza it is easy to show direct communication among the diseased individuals, but, keeping the possible errors in mind, if we examine the available evidence, we shall come to the conclusion that there is an enormous number of observations to establish without doubt the fact of direct transmission to the exclusion of all other explanations.

The contagious character of influenza is seen when it breaks out in a large family, in which, as a rule, the remaining members of the family follow the originally affected individual in quick succession. "Mirum est totas civitates repente occupari et ubi unus corripitur aliqua in domo statim singulis ejus familiæ malum communicari" (Mercurialis, 1580).

The evidence of the above-mentioned rule is greatest at the beginning of the epidemic and when it is dying out, and is least during the height of the epidemic, at which time many opportunities for contracting influenza outside of the house exist.

It is, therefore, easily explicable that influenza often enters the household in a vehement and miasmatic manner, simultaneously affecting all. "Non unus vel alter de tota familia sed fere omens eodem momento lecto decumbere debuerunt" (Juch, 1742).

But there are also exceptions to this rule, for the remaining members of the family, in spite of their intimate contact with the diseased individual, frequently remain exempt. In the English statistics (Parsons' report) many such exceptions are mentioned, and many English physicians even emphasize the fact that, as a rule, there is only one case at a time in a family. At the time of the pandemic this was only exceptionally the case, but in the less contagious after-epidemics it was more frequent.

In the following examination of the distribution of influenza in closed institutions, upon ships, and in hospitals, we shall frequently meet with noteworthy exceptions to the rule—that is to say, we shall find many instances of immunity from influenza, in spite of the implantation of the same within narrow confines. We must, therefore, once for all emphasize the fact that in this respect influenza acts the same as any other contagious infectious disease, like diphtheria, scarlet fever, measles, etc. These exceptions to the rule surprise us in the case of influenza only because we think of this disease as a highly contagious pandemic affection. But not every one who is affected by influenza distributes its contagion, and not every one disseminates fully virulent germs. Cases characterized by exclusively nervous or gastro-intestinal symptoms, without secretion products from the respiratory mucous membrane, are very likely harmless. Another case may disseminate germs which perchance do not come in contact with the surrounding individuals. Chance acts as a very important factor in the distribution of contagious diseases.

But in spite of exceptions the rule remains that the patient gives off virulent germs in such numbers that his whole family, his household, and all who come in contact with him are immediately infected.

The literature, especially of the last pandemic, is replete with examples which prove the importation of the disease from an infected area into one which had not been infected. Small towns, villages, hamlets, farms, passes, ships, and inclosed institutions furnish the most cogent proofs.

On innumerable occasions it has been shown that an individual returning from afar to his own village or farm, itself far removed from external communication, had imparted the disease, at a time when for far and wide around there was no influenza. After the infection of the members of the family of this individual, the tenants of the house contracted the disease, and the subsequent development of the pest could be easily traced, in the smaller places, as radiating from this original focus. The English collective investigations of 1782 already called attention to such cases of importation and infection from influenza. We will mention a few examples:

A good field for observation was London, to which daily crowds of persons travel by rail in order to attend their business, returning again in the evening to their houses and villas. With an unusual monotony the following sentences occur again and again in the English Collective Investigation, namely: "The first case of influenza was a man who went to London daily," or "All the earliest cases were men going to London daily, their wives and families being affected later." The weekly markets and fairs in England played an important part in the dissemination of the pestilence from city to country. More rarely than one would suppose did the first cases of influenza in a place begin in a hotel (Lübeck, Strassburg, Davos).

A physician leaving Berlin on the seventh of December was taken ill at his home, Elgersburg (Thüringen), with influenza, on December 8, but, notwithstanding, made several visits in his native town. A few days thereafter those visited by him were taken ill, Elgersburg and its vicinity up to that time not having had a single case of influenza (P. Friedrich, *loc. cit.*).

On January 4, 1890, an owner of a slate quarry returned to his home, Llanegryn, ill with influenza, from London, where he had lived in a house infected by the disease. On January 6 nine other inmates of the house where he had lived in London, and five to six days thereafter the workmen of the slate quarry, were taken ill (Parsons' report, *loc. cit.*).

In quite a number of cases Pribram could accurately trace how persons ill with influenza coming from Vienna, in which city the disease was prevalent, to the city of Prague, which was still exempt, infected their relatives and other inmates of the houses where they lived.

Duflocque describes how, on December 6, 1889, a lady returned from Paris, which was infected, to a village still free from the disease. She was taken ill on December 8; her coachman became ill on December 9; her child on December 11; its nurse on December 13; the chambermaid and a man-servant on December 14; on the thirteenth a seamstress who had brought clothes into the house; then the father, mother, husband, and daughter of the seamstress. Within a further eight days influenza became disseminated throughout the whole village.

Similar examples occur in large numbers in the literature of all countries, especially in the full official Swiss reports of F. Schmid.

Moreover, convincing observations regarding the dissemination of influenza by contagion are afforded by persons who winter on lonely mountain-tops and passes. We know of no example—and one such example, proved with certainty, would be of the greatest significance for the aërodromal theory of influenza dissemination—where people, entirely removed from communication, or wintering upon mountain-tops, were stricken with influenza. In every instance where such individuals had become affected personal communication with those ill with influenza in the valley could be demonstrated.

The significance of these instructive investigations, particularly those emanating from Switzerland, has been exaggerated by some contagionists.

It is going too far to deduce the non-dissemination of influenza through the air from the fact that the isolated inhabitants on the mountains of Switzerland have not been attacked. It is quite conceivable that the germs of the disease which emanate exclusively from influenza patients are contained in the air of infected houses and cities, and that they also distribute themselves within certain limits through the air, without imagining that these germs can also be carried to mountain-tops at an elevation of 2000 meters or more. Those who look upon influenza as a miasma of a vapor sinking down toward the earth from the air, have their views contradicted as much by the observations on mountain-tops as by all the other facts regarding the dissemination of influenza.

If the mode of dissemination of influenza in Switzerland is studied in detail, it will be found to conform to the conditions of communication in that country. As far as the mountain passes are concerned, the routes traversed during the winter by the mail conveyances (Julier Pass, Great St. Bernard, Engadine, etc.) early showed numerous cases. The official Swiss report of F. Schmid contains an abundance of highly interesting details. We will quote some examples of the transportation of the disease to high altitudes:

A whole colony wintered on the Rigi (1800 meters). After the disease had been imported by a painter returning from Lucerne, most of the Rigi inhabitants were afflicted.

At the Grimsel Hospice (1375 meters), the watchman, returning from the valley where he had associated with influenza patients, was first taken ill. Two days thereafter the other watchman, who had not left the Hospice, contracted influenza.

In Arosa the physician was the first one to contract influenza immediately after his return from the infected Davos. In rapid succession the inmates of the physician's house became infected, and then those of other houses of Arosa.

In Davos the disease started from the Hotel Schweizerhof, where a recent guest was the first to become afflicted. Two persons who occupied the rooms adjacent to his next became ill, and finally there was a general infection of the whole locality.

The official report of the Austrian Chief Board of Health emphasizes the fact that only such inhabitants of mountainous altitudes as had associated with the infected inhabitants of the valley were infected by influenza.

A series of important facts proving the contagiousness of influenza is given by the observations on the dissemination of the disease upon ships and by means of maritime communication. From the enormous amount of material, and especially from that contained in the British marine report, the following conclusions may be drawn:

1. In those extra-European continents and islands which were infected by influenza the harbors and coast towns were first attacked by the epidemic. Frequently the ship importing the pestilence was identified.

2. Upon ships which, after voyages of weeks, touched at an infected port, there followed an outbreak of influenza a short time after the arrival at that port or a few days after leaving it. The following are but a few of the numerous examples:

Leith, the harbor of Edinburgh, and Hull in England were infected by ships' crews from Riga.

An American man-of-war brought influenza to Gibraltar, and a training-ship conveyed it very early (December 15) to Spezia, which was one of the first places in Italy to be attacked. Already in the first week of January influenza was carried by a ship to the southern point of Africa, Cape Town.

At a time when influenza had not yet affected any harbor of the eastern coast of Africa, the French corvette "D'Estaing," severely infected with influenza, arrived in the middle of March at Zanzibar. On March 19 the commander of the French ship, still suffering from the sequelæ of influenza, made his official visit to the "Sperber." Two days thereafter influenza broke out upon the "Sperber" and also upon land, among the employees of the East African Company who had been in communication with the "D'Estaing" and the "Sperber." The ship "Carola" arrived in Zanzibar from a healthy district and communicated with the infected "Sperber," with the result that on April 1 the disease also broke out on the "Carola."

Influenza broke out on the training-ship "Bretagne," lying in the harbor of Brest, two days after an infected officer had returned on board. Of the 850 persons on the ship, 244 successively became infected. Later still another training-ship, the "Borda," became attacked, while other ships lying in the neighborhood of the "Borda" and the "Bretagne," but having no communication with the latter, remained exempt. The officers of the infected ships, who on account of their illness were granted leave of absence home, carried the disease first to their families, and later on the whole city of Brest became infected. The mail steamer "St. Germain" left St. Nazaire on December 2, touched on December 5 at Santander, and here received on board a traveler from Madrid, where influenza was prevalent, the crew of the ship, however, being in the best state of health. On the following day the traveler was taken ill with influenza; and four days later, the attending physician. Within two more days the disease spread with such rapidity throughout the whole vessel that out of the 436 passengers, 154 were taken ill, besides 47 sailors.

The troop ship "Himalaya" arrived on January 30 at the uninfected harbor of Colombo (Ceylon) with 19 cases of influenza on board (during the voyage 140 cases had occurred). On February 7 the epidemic broke out in the harbor, first among the pilots employed there.

It is worthy of mention that influenza did not break out on ships in an explosive manner, but became slowly disseminated. On several ships the epidemic lasted for many weeks.

In some few instances the duration of the epidemic on ships, for example, on the "Bellerophon," from March 27 to April 30; upon the "Canada," from the eleventh of April to the twenty-fourth of May; upon the "Comus," from the tenth of April to the third of May, may be explained by the fact that the affected ships, which in the course of their voyage became free from the disease, arrived at infected ports, at which places they took up fresh influenza germs.

The German marine report, in reference to the spread of influenza upon ships, sums up: "In every case upon our ships the disease did not appear suddenly, but gradually; not until after the sixth day from the beginning of the epidemic did the cruiser "Schwalbe" have numerous cases on board."

We must not ignore the fact that in not a few cases the experiences of other ships were quite different from these, for, just as upon the land, in some cases the disease arose suddenly and with great vehemence. Upon this fact the upholders of the miasmatic theory lay great stress.

We will content ourselves by giving one example—the celebrated case of the frigate "Stag"; upon this ship, on the third of April, 1833, as it reached the infected coast of Devonshire and so "came within the land breezes," the epidemic arose suddenly with great vehemence. At 2 o'clock 40 men were sick; at 6 o'clock this number was increased to 60, and on the next day, at 2 o'clock, that is, within twenty-four hours, 160 men were affected by the disease. In regard to this case, which is one of the favorite examples of the spread of influenza germs through the air, Parkes remarks very pertinently that the report is incomplete, in so far as it does not state that there had been no communication with land (Plymouth or Falmouth). Moreover, the direction of the wind as recorded does not correspond.

Upon the Netherland frigate in the harbor of Macassar (on the island of Celebes) an influenza epidemic arose in February, 1856, which "within a few days" affected 144 men out of 340 of the entire ship's crew. On the "Canopus" (650 men), which in 1837 was in the harbor of Plymouth, where influenza was present, on the fifteenth of February "two-thirds of the entire crew were suddenly stricken with influenza." Upon the Swedish corvette "Saga," at the end of January, 1890, during the day, after the diseased had left the infected harbor of Havana, influenza arose suddenly with such vehemence as to almost bring about a catastrophe.

The morbidity upon ships of both the German and the English navies in general was slight. It was about 3 per cent. upon the "Benbow," belonging to the Mediterranean fleet; about 6 per cent. upon the "Imperieuse," etc. But there are many examples of a much higher morbidity, as of 60 per cent. upon the "Archer" and 57 per cent. upon the "Curacao."

More important than the observations mentioned above is the fact that in our latest influenza period, in spite of the development of facilities for obtaining news rapidly, no single example was brought to light of a ship upon the high seas becoming affected *ex aere*, without touching at infected harbors or coming in contact with infected ships. Several cases where this is said to have happened were mentioned in the last century (at first by Reaumur in 1732). These have attained a historic notoriety, and still serve as support for the upholders of the panaërodromic theory.

But all these cases, that of the "Atlas" (1780, in the China Sea), of Kempenfeldt's squadron (1782, off the Lizard lighthouse), of Lord Howe's fleet (1782, off the Dutch coast), of the frigate "Stag" (1833, off the English coast), of the "Arcona" and the "Ariadne" (1785, in the China Sea), cannot, as Parkes has shown, stand the test before strict criticism.

On this account the following case, which occurred in our most recent pandemic, deserves attention. Upon the French man-of-war "Duquesne," in February, 1890, fourteen days after leaving the harbor of Montevideo, while the vessel was upon the high sea (150 miles from the American and 700 miles from the African coast) and in fine weather, a most intense epidemic of grip arose; out of 580 of the crew, 233 were taken ill. Even although Montevideo was free from grip and was not, like Buenos Aires, Santos, etc., affected in the beginning of February with the disease, nevertheless the case of the "Duquesne" is interesting. The explanation of this case lies in one of two facts: Either there were mild influenza cases on board at the time of sailing which at first did not attract attention because they did not report themselves ill, or the germ was carried on board in merchandise, clothing, etc., which, when unpacked, fourteen days after leaving Montevideo, spread the disease on the ship.

The English marine report teaches us that the greater number of ships upon the ocean during the epidemic period of 1889–1891 suffered from influenza. This is easily explained. Infected ships communicated the disease to harbors at which they arrived, and ships previously free from influenza were there infected. The intercommunication of ships from harbor to harbor throughout the world makes a closed circle of mutual infection analogous to that resulting from railroad traffic on land.

INFLUENZA IN INSTITUTIONS (PRISONS, ETC.).

These institutions furnish the best and most favorable field for studying the origin and the transmission of the disease from the first case. Official and private observers in all countries have carefully gathered data from these sources on which to base reliable statistics. P. Friedrich and Parsons have collected an enormous material bearing on these points. The most important points are:

Those institutions which were relatively most shut off from communication with the outer world, namely, the prisons, showed a remarkable immunity against the invasion of influenza.

Lancisi had already observed this in the epidemic of 1709 in Rome, and reports that the prisons of the Holy Inquisition remained free of the disease. A large number of prisons (in Germany 21 can be enumerated) remained entirely free of influenza in 1889–1890. Quite frequently—in not less than 39 institutions—the same thing was observed in England, where the prisons remained without a single case, although lying in the midst of towns like Portsmouth, Kendal, and others, which were markedly affected by the disease.

Clae Linroth noted the same condition in Sweden, and we agree with him when he says: "Influenza makes its way more easily over a space of from 500 to 1000 kilometers than it does over the small barrier of a prison wall."

Next to prisons come certain strictly secluded convents. Their walls also occasionally gave remarkable protection. A convent in Charlottenburg which was guarded most strictly from communication with the outer world, containing nuns and 100 other female inhabitants, remained entirely free from the epidemic of 1889–1890 (A. Hirsch). The same condition occurred in some other similar convents and monasteries.

Nearly always in prisons, asylums for the insane, and in a large number of other relatively closed institutions, was it observed that the first cases of influenza in these places occurred in servants, nurses, overseers, and officers having free communication with the outside world, or in new arrivals. Not until later were the prisoners, lunatics, etc., affected. In a great number of these institutions, especially in prisons, cases occurred among the officers and servants only, in some instances attacking every one of them, without a single case appearing among the inmates of the institution. This condition occurred in the prison in Braunschweig; in the Central Prison of Glogau; in the prisons of Norwich, Bodmin, Winchester, and Lewes in England. In almost every case the morbidity of the officers and servants of the affected institutions was much greater than that of the inmates.*

In the Franciscan convent at Reutberg, which is strictly closed against the outer world, the first cases occurred in the two doorkeepers of the institution, and not until several days afterward were one-half of the remainder of the inmates of the convent affected.

In the lunatic asylum at Erlangen cases of influenza occurred during the period from the twenty-first of December, 1889, to the eighth of January, 1890—that is, for eighteen days continuously. These cases occurred exclusively among the officers, physicians, and nurses who came in contact with the outer world. Not until after these had been affected did the epidemic arise among the insane.

Among the 1112 insane in the institution at Palermo, 7.8 per cent. were affected. Of the 260 employees of the institution, 62 per cent. were affected. Numerous similar examples might be quoted from German, French, English, and Swedish literature.

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* Compare the tables of P. Friedrich.

With conspicuous frequency the prisons, and to a certain extent also the lunatic asylums, were affected at a considerably later period than their environs.

This was the experience in the prisons at Sagan, Ludwigsburg, Strassburg, in the asylums at Lengerich, Wallingford, etc., at Hagenau i. E., at which places influenza arose in the middle of December, but the first cases were noted in the jail on the twentieth of January and in the prison upon the twenty-second of January. Numerous analogous observations might be mentioned from the collective English investigations.

But no human being lives his life entirely secluded from the outside world, and so the isolated convents and prisons (separate cell prisons) could not often withstand the inroads of influenza. Once introduced, the morbidity of influenza was in many cases very considerable (in the jail at Wasserburg, 84 per cent.; in the separate cell prison at Freiburg, 30 per cent., of the inmates were affected). Nevertheless, we find, in carefully examining the statistics of Germany and England, that the morbidity in prisons and lunatic asylums, to which we may add the convents as closed institutions in the narrower sense, was decidedly less than the morbidity in open institutions, such as orphan asylums, seminaries, nursing institutions, deaf and dumb asylums, etc., to which influenza was carried much more easily, and where the free communication between the inmates of the institution provided a suitable soil for the disease. On analyzing the tables I find that the average morbidity in the Bavarian prisons amounted to 31 per cent.; in all the other German prisons, 26 per cent.; in the insane-asylums, 17.7 per cent.; while in the above-named open institutions the average morbidity was never less than 58 per cent. The morbidity in the English prisons was decidedly less than in the German ones. It amounted, for example, in Strangeway (1000 prisoners), to 7.7 per cent.; in Wandsworth (1043 prisoners), to 18 per cent.; in Pentonville (1126 prisoners), to 7.6 per cent., etc.

We have good reason also to consider influenza in hospitals. Hospitals do not really belong to the class of closed institutions in which they are usually included. They are, on the contrary, open institutions (visitors). Further, they are ever a resort of numerous influenza patients, and hence are most liable, throughout the duration of the epidemic, to be in the highest degree a favorable place for contagion. One would have anticipated, for this reason, that in all hospitals where isolation of influenza patients could not be carried out, the contagious character of the disease would have shown itself in the frequent affection of the inmates of such hospitals. This has not, however, by any means been the case. A large number of the largest hospitals, in the years 1889–1892, were almost entirely free from influenza inside the house, although the influenza patients were freely distributed among the other patients.

This was the case in the City Hospital at Cologne, which has 700 beds. Altogether there were 439 influenza patients; the maximum daily number in the hospital at the height of the epidemic was between 132 and 144 influenza patients, yet only 13 patients became affected in the hospital, whereas one-half of the doctors and one-third of the nurses were affected. Conditions similar to these were seen in the Jacobs Hospital in Leipsic, in the Friedrichshain Hospital in Berlin, in the Municipal Hospital at Meissen, in the City Hospital at Halle, in the Allerheiligen Hospital at Breslau, in the Garrison Hospital at Kolmar, in the hospitals at Pirmasens, Fulda, Schöngau, Blankenheim, in the hospitals and maternity institution at Giessen, in the University Hospital at Zurich (Eichhorst), in the General Hospital at Nottingham, Warrington, Bridgend, in the hospital "Sabbatsbergen," and in other hospitals of Sweden (Warfvinge). "The character of the influenza in my wards," says Drasche, "had not the slightest semblance to an infectious disease."

In strong contrast to these hospitals which remained immune, several others might be mentioned where influenza took root and where the inmates of the hospital showed a considerable morbidity.

In the hospitals at Heidenheim, Cologne, Coburg, Buxtehude, Schopfheim, Münsingen, nearly all the inmates were attacked. In some hospitals "the progress of the disease could be traced from bed to bed, or the transmitters from ward to ward identified"(?), as in the Medical Clinic at Würzburg, in the Garrison Hospital at Stuttgart, in the hospitals of Nuremberg, Bamberg, Charlottenburg, and in the Kensington workhouse and infirmary.

We find the same contrast as regards morbidity, and we might add, as regards the duration of the epidemic, if we examine the distribution of influenza in other relatively closed institutions, as, for instance, orphan asylums and reformatories, although in the German institutions of this kind, as the statistics of P. Friedrich show, an enormous morbidity was so much the rule that in order to study the rarer but not less striking exceptions, we must turn to the English statistics. Only a few examples will be quoted here:

In the Forest Gate District School (London), from the twenty-ninth of November, 1889, to the ninth of January, 1890, among 576 children only 29, that is to say, 5 per cent., were attacked, whereas in the South Metropolitan District School (Sutton), which was made up of a like class of children, in which the epidemic lasted only twelve days, among 1850 children, 615, or 33 per cent., were affected. In the King Edward's School (242 scholars), in an eleven-day epidemic, 177 boarders, or 73 per cent., were affected.

On the training-ship "Boscawen," from the nineteenth of January to the tenth of February, among 500 boys varying in ages from twelve to eighteen years, only 13, *i. e.*, 2.6 per cent., were affected. On the training-ship "Exmouth," among 528 boys during a thirteen days' epidemic, 381, or 75 per cent., were affected. Numerous similar examples showing these strong contrasts could be quoted.

If we then take a survey of the behavior of influenza in families, upon ships and mountains, and in closed institutions, we see that there is a considerable number of facts to demonstrate conclusively the contagious nature of influenza. But we have also seen numerous remarkable exceptions to this rule. We must not close our eyes to these facts, nor act like the supporters of the contagium theory, who quote only those facts which suit their theory, while omitting any antagonistic observations. The exceptions are too frequent to be accidental, and many of them are very important. Even if in the question of the contagiousness of the disease one positive case proves more than numerous negative ones, we must, nevertheless, try to inquire into the reasons for the apparent contradictions existing in many cases, to discover the concealed ways of the infection, and to ascertain the conditions which determine at one time rapid communicability and dissemination, at another, true fixity and sterility. At the present time we are very far from an exact knowledge of the more intimate nature of the contagion, which would enable us to take more effective measures of prophylaxis and disinfection.

I can only explain these opposite conditions by the assumption that there are two principal kinds of contagion—a slowly spreading form, in which the disease germs remain adherent to the mucous secretions of the patients, and in this way are disseminated only slowly and gradually, and occasionally may be rapidly destroyed; and an explosive form, in which the dried secretions which carry the germs are wafted as dust into the air, and in this way may simultaneously reach all the inhabitants of a house, a ship, or an institution. I find that many English and French contagionists consider that "upon the concentration of the infective principle in the air" depends the sporadic or epidemic character of the disease.

MORBIDITY AND MORTALITY.

Among all infectious diseases there is none which affects the entire population, irrespective of age and condition, in so short a time as pandemic influenza.

An enormous morbidity with a relatively very small mortality is one of the preëminent characteristics in the epidemiology of pandemic influenza, and a sign of great assistance in judging doubtful epidemics of preceding ages. Remarks like "vix unus evasit," "nemini pepercit," "correpti sunt fere omnes," occur everywhere in the writing of the older authors, together with the remark that except the aged, the weakly, and the phthisical, no one died of the disease.

The mass of figures that has been accumulated in collective investigations and official reports as regards the question of morbidity rests largely upon estimated numbers by medical observers. No wonder, then, that the figures vary considerably, even from the same districts.[*] There is, however, no doubt that considerable differences in the percentage incidence existed in different localities. The majority of the 3304 reporters to the German collective investigations agreed upon a morbidity of from 40 to 50 per cent. of the population in their respective districts.

Similar averages were arrived at in St. Petersburg, Paris, and Budapest (50 per cent.), Vienna (30 to 40 per cent.), Massachusetts (collective investigation, 39 per cent.), and Antwerp (33 per cent.). In France the influenza morbidity was calculated by the statistician Bloch to be 75 per cent. of the entire population. The figures (in nearly all cases above 50 per cent.) of the Swiss report for the various cities and districts of that country are very high. In contrast to this are the figures from Munich, calculated on the medical notifications, not very reliable for this purpose—22 per cent.; and London, 34 per cent. Parsons tells us that the morbidity in London in the epidemic of 1782 amounted to three-quarters of the population; in 1837 to one-half, and in 1847 to one-quarter, of the entire population, and that in the epidemic of 1889–1890 it certainly did not amount to more than one-quarter of the entire population.

The period of estimates was followed by a period of statistics, and now a considerable difference was revealed. The influenza morbidity of the various workmen's clubs, of the officials and servants of the postal and railway systems, and in England too among the large banks and business houses, was almost always considerably less than that estimated by the medical attendants. The following extract from the statistics will show this:

The morbidity amounted to—

Ortskrankenkasse, Berlin (258,090 members)	1.7 per cent.
Betriebskrankenkasse, Berlin (24,454 members)	3.2 " "
Ortskrankenkasse, Strassburg (5692 persons)	6.2 " "
Eisenbahnkrankenkasse, Strassburg (903 persons)	14.7 " "
Factory population, Alsace-Lorraine (18,620 persons)	24.7 " "
Employees of Bavarian state railroads (12,718 persons)	22.0 " "
Day-laborers on Bavarian railroads (14,213 persons)	23.0 " "
Chief Postal District of Dresden (2927 persons)	17.4 " "
Number of factories in Baden (3140 persons)	30.0 " "
Rural District Segeberg,[†] Schleswig (18,216 persons)	33.0 " "
District, Triberg[‡] (11,054 persons)	35.0 " "
Collective investigation in Strassburg[§] (2379 persons)	36.5 " "
Factory workers of the Parish of Triberg (1791 persons)	44.2 " "
General post-office in London (6872 persons)	33.6 " "
Bank of England (1117 persons)	20.8 " "
London and Westminster Bank (502 persons)	21.0 " "
Great Eastern Railway (15,261 persons)	13.8 " "
London and Northwestern railway (59,731 persons)	6.4 " "
German army (including navy)	10.0 " "

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[*] Compare Rahts, "Deutsche Sammelforschung," p. 48, P. Friedrich, *loc. cit.*, p. 181, ff.

[†] Local collective report.

[‡] House to house count.

[§] Collection of a number of seminaries and factories, including police and street railway employees.

The remarkably slight mortality just quoted in several of the sick-clubs, etc., is unquestionably due to the fact that many persons who were only slightly affected continued their work or only remained idle for a very few days, and were thus excluded from the statistics. Similar circumstances probably explain the strikingly small statistical morbidity of the German army.

A very different picture is shown by the schools, seminaries, pensions, orphan asylums, workhouses, etc. A glance at the comprehensive statistics of P. Friedrich,* Parsons, Schmid, and others shows us that these institutions had an enormously high morbidity—usually 60 per cent. and over. The statistics of all countries show the same (Combe,† Comby‡).

The general impression which one receives after looking into the interminable morbidity statistics is that the estimates made by the German doctors quoted above were not too high. If, in addition, we remember that many slight cases did not come under the observation of any medical attendant and were not included in the statistics, we shall not err greatly in concluding that the epidemic of 1889–1890 affected about one-half of the inhabitants of Germany.

That the general morbidity in the later epidemics did not approach that of the pandemic every one has had the opportunity of observing. The same thing is proved by the numerous statistics of Germany and England (Wutzdorff, Parsons).

In these after-epidemics also the schools, orphan-asylums, pensions, workhouses, etc., still show a decidedly greater morbidity than the general population.

As regards the so-called miasmatic explanation of the suddenness of the general infection, we must refer to what we have previously said (p. 544). Even if the epidemic of 1889 did not begin in the explosive manner generally accepted, so that "every one was affected at the same time," even if, as was proved, isolated cases everywhere preceded the epidemic outbreak, yet there is no doubt that a rapid development of the epidemic often did occur in the form of a sudden infection of the population.§

Examples of this occurrence are found in great number in the history of influenza and also in the last pandemic. We would refer to our remarks above in reference to the frigates "Stag," "Canopus," and "Saga" (see p. 559); also to the epidemic of the Grands magasins du Louvre,

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* See pages 210 and 237, *loc. cit.*

† "Zeitschr. f. Schulgesundheitspflege," 1890, p. 505.

‡ "Revue mens. des maladies de l'enf.," 1890, p. 144; cf. Ripperger, *loc. cit.* p. 205 ff.

§ A fact which cannot be simply neglected, as several enthusiastic contagionists have done. See the curve (Plate VIII), and also the instructive curves of Ripperger.

1889, in Paris (see p. 576). We may add the following examples: In the Baltic mill at Neumühlen, near Kiel, within two to three days, out of 350 workmen, 150, or 43 per cent., were affected. At the machine factory in Mühlhausen, in Alsace, with from 3000 to 4000 workmen, 750 were attacked in a single day. In the industrial school at Swinton, near Manchester, during an epidemic of thirteen days, of 589 children living in the same rooms, 171, or 29 per cent., were affected, and in the following sequence: first day, 5; second day, 71; third day, 30; fourth day, 7, etc.

Of course, these examples in no wise contradict the contagion theory; they seem, however, to prove that the germs in isolated districts were occasionally aërodromic, and were able to produce simultaneous infection in large numbers, or, in other words, sudden affection of the masses.

Simple, uncomplicated influenza is a disease which is but rarely dangerous to life. Since in an epidemic the number of uncomplicated cases is very high in comparison with that of the cases which end fatally from complications, the mortality in comparison to the incidence is very slight.

The mortality in the epidemic of 1889–1890 was as follows: In Munich (22,072 cases), 0.6 per cent.; in Rostock (3568 reported cases), 0.8 per cent.; in Mecklenburg-Schwerin (21,000 cases), 1.2 per cent.; in Leipsic (12,769 cases), 0.5 per cent.; in the Germany army (55,263 cases), 0.1 per cent.; in Karlsruhe (43,000 cases), 0.075 per cent.; and in 15 Swiss towns, 0.1 per cent.

But such statistics have only a slight value, and they do not give a correct representation of the mortality produced by influenza, because the numerous fatal complications and sequelæ, especially the deadly influenza pneumonia, are not included, as they should be, in the influenza mortality. But the deaths from these causes appear very plainly in the rise of the general death-rate.

Everywhere, soon after its epidemic development, influenza produced an increase, and almost everywhere a sudden increase, in the death-rate. The date of this sudden rise of the total mortality proved a valuable aid in determining the time of the outbreak of the epidemic in the different cities of Germany, as P. Friedrich has shown in his statistical investigation.

Naturally this is not the place to go into statistical tables, but a few examples of some of the large cities may be quoted to show the general increase in the mortality at the height of the epidemic of influenza. If we compare the highest, therefore the acme of the influenza epidemic of 1889–1890, that is, the weekly mortality number,* with the same week of the year 1888–1889, which was free from the epidemic, we have the following comparative figures for these cities:

Berlin, 20.6 : 37.7; Hamburg, 24.2 : 32.1; Breslau, 29.2 : 30.0; Leipsic, 20.7 : 41.7; Munich, 24.6 : 48.6; Cologne, 31.9 : 52.2; Dresden,

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* Calculated for 1000 inhabitants and for the year.

19.5 : 38.8; Frankfort a. M., 20.2 : 41.4; Kiel, 23.3 : 69.6; Strassburg, 24.8 : 52.5; Stuttgart, 23.1 : 49.0; Brussels, 29.5 : 52.4; London, 24.9 : 32.4; Paris, 22.3 : 61.7; Vienna, 52.8 : 45.9; and in 15 Swiss towns, 23.1 : 47.9.

The following table shows the total number of deaths in Paris, arranged by weeks for the years 1888–1889, in comparison with the epidemic years 1889–1890. The numbers in Paris were*:

	1888–1889.	1889–1890.
November 11 until November 17†	873	917
" 18 " " 24	806	968
" 25 " December 1	876	1020
December 2 " " 8	942	1091
" 9 " " 15	984	1188
" 16 " " 22	982	1626
" 25 " " 29	955	2374
" 30 " January 5	970	2683

The increase in mortality during an epidemic of influenza, as shown by the statistics, is mainly due: First, to an increase (in some cities nearly double) in the mortality from acute diseases of the respiratory organs, and, secondly, to an appreciable rise in the death-rate from pulmonary tuberculosis. ‡

With the disappearance of the epidemic a slight diminution in the general death-rate and partly also in the mortality from acute diseases of the respiratory tract may be noted. The mortality from pulmonary tuberculosis especially fell so low that the total mortality from this affection in the year 1890 showed no increase, or only a slight one, above the average. Many phthisical patients who would have died in the epidemic year only succumbed somewhat sooner from the prevalence of influenza than they would have done without its influence.

The increase in the general mortality during the influenza epidemic furnishes the best standard for estimating the total number of deaths. This calculation has been attempted with the help of the increase in the general mortality. Sperling, basing his calculation on the mortality tables of 200 German cities (11,500,000 inhabitants), found that in the whole of Germany (49,500,000 inhabitants) about 66,000 persons succumbed to the epidemic of 1889–1890 (or 1 per 1000 of the population).

Not only in the number of deaths does influenza show its influence upon the population, but, like all great epidemics, it also has an influence in diminishing the number of births. A. Bloch showed that in France the number of births in the epidemic year of 1890 was 42,500 less than in 1889. The decrease in the number of births occurred especially in the months of September and October, 1890, corresponding as regards conception to December and January, at which time the disease prevailed in France. In the earlier months the disturbing influence of influenza upon pregnancy shows itself in abortions and miscarriages. A similar influence on the birth-rate was shown to exist for Germany by Sperling and Friedrich; for Bavaria, by Stumpf; and for Switzerland, by Schmid.

Sperling showed that in the epidemic year (1890) there were 18,800 births less than in an average year. He calculates that through the influence of influenza in 1889–1890 the total loss of life (deaths plus decreased births) in Germany amounted to 85,100 individuals.

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* Reuss, "Annales d'hyg. pub.," 1890, No. 2.

† Beginning of the influenza epidemic in Paris, November 17.

‡ See the statistics of P. Friedrich.

Moreover, there exists also much statistical material from the epidemics following the pandemic, especially for Germany and England. We cannot go into detail, but it may be mentioned that the influenza mortality in the years 1891 and 1891–1892 in both countries was greater than at the time of the pandemic (due to the longer duration and especially to the much more malignant character of the after-epidemics).

According to the official reports of both countries, the deaths from influenza were:

1890 in Prussia	9,576	In England	4,523	persons.
1891 " "	8,050	" "	16,686	" [*]
1892 " "	16,686	" "		" [†]

The number of deaths from influenza in London amounted to:

From January to March, 1890 (pandemic)	558	persons.
" May to July, 1891 (second epidemic)	2,104	"
" January to March, 1892 (third epidemic)	2,078	"

Quite a number of important conclusions can be drawn from the statistics in regard to danger to life at different ages. The following apply to all the epidemics: First, that the general mortality of children under one year was either not at all, or only slightly, influenced by influenza; and this observation applies also to infant life generally; second, that the greatest mortality from influenza occurred in the aged.

This is true only of the statistics from Germany. The English statistics, on the other hand, in the last epidemics, as well as in the earlier ones, from 1837–1838 and from 1847–1848, show a decidedly greater mortality among children under one year and in children of from one to five years of age, as compared with the later years of childhood or adolescence. F. Schmid arrived at the same conclusion from his laborious statistical investigations in Switzerland. Since the statistics of both England and Switzerland, which agree also with the German statistics, show that the morbidity of early childhood is a remarkably low one, the conclusion must be drawn that influenza is most dangerous in early child-life, as well as old age. But this is in direct contradiction to the statements of most of the observers, for they have especially called attention to the harmless and light character of influenza in patients at this age. There are then contradictions between general experience and the statistics of England and Switzerland which are at present inexplicable.

[*] Two epidemics: in the spring and in the fall and winter.

[†] Not mentioned in Parsons' statistics.

INFLUENCE OF AGE, SEX, AND OCCUPATION.

No age can be said to confer immunity against influenza. In spite of the contradictory statements regarding age incidence, it would appear, from the majority of opinions of physicians and from the statistics, that the following statements may be taken as correct:

1. Children at the breast were affected to a much less degree than all other ages.* There is not much foundation for the very general opinion that influenza at this age occurs in so mild a form as to remain unobserved, and is consequently not included in the morbidity statistics.

2. School age, adolescence, and middle life are the periods especially and almost equally affected by the disease. The years from twenty to forty, however, show the greatest incidence.

3. Old age, reckoned from fifty upward, is distinguished by a lessened morbidity.

The established statistical fact of the frequent affection of school-children is probably explained by the fact that the school is a principal focus for the distribution of contagious diseases. The statement that in some, usually small, places the "children" were affected earlier or even exclusively, or that during childhood showed the greatest incidence, is to be found in reference to both the earlier and the more recent epidemics. In most of these cases of this sort probably the school epidemics gave the impression of greater liability of children.

Yet infants are not entirely immune. In the lying-in hospital at Giessen, during the epidemic of 1890, 8 out of 20 infants became affected by influenza (Strassmann), and in the literature many cases are reported where infants had influenza at birth, which seems to point to intra-uterine infection (?).

In February, 1891, in a few places in the district of Münster, influenza attacked school-children especially. At Standish, in England, the epidemic began in October, 1891, beginning among children, and in a few days affected 100 of them; not until November were the adults attacked. A similar example has been previously mentioned. It is questionable whether the disease was true influenza. With even greater skepticism do we regard the reported observations that children and infants at the breast and very small children were specially affected.

The accompanying age-curve (Fig. 38) shows the relative ages of patients affected by influenza in Munich in the year 1889–1890 in 22,972 cases. The continuous line shows the percentage attacked at any age; the dotted line shows how many per 100 inhabitants of

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* "Children in general escape; I have heard of no child at the breast having it" (Campbell, Mease, Kirkland, and others, 1782). "Les enfants du premier age en ont paru à peu près exempts" (Vicq d'Azyr, 1782). Babies in the maternity institutions at St. Gall, Basel, Aarau, Zürich were not affected by influenza, in spite of the fact that they were nursed by influenza-affected mothers (F. Schmid).

Munich belonged to the age in question. (Based on the census of 1885.)

This Munich curve justifies what we have briefly mentioned in regard to age. The carefully compiled statistics in regard to age, made by the doctors in Hesse and the district of Mainz, and the Swiss statistics of F. Schmid, also bear out these statements.

In opposition to the above almost universally accepted opinion of the special predisposition of adolescents to influenza are the statistics of the German and English armies. The former had a morbidity of 10 per cent.; the latter, of only 6.2 per cent. Several Prussian garrisons (5 per cent.) and numerous English ones (27 per cent.) were not affected by influenza at all, although of the latter many were situated in the midst of severely infected cities. It is further noteworthy that the German army report especially mentions that in the large majority of German cities the military was affected much later by influenza than the civil population. The same condition of affairs prevailed in France (Arnould). Friedrich explains this exceptional condition by the "usually slight communication" between these two classes of the population. But this circumstance should have been more than compensated for by the aggregation, in barracks, of large numbers of people of the predisposing age.

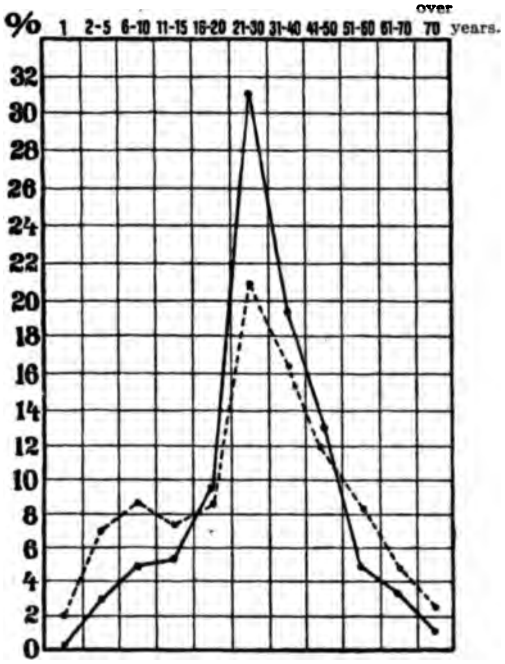

FIG. 38.

As regards sex, there is no difference of predisposition. The occasional statistical differences that occur are explicable on other grounds. It is evident that the male sex, having more intercommunication, would show a larger number of cases than the female, who stay more at home, and that the family more often caught the disease from the father than the mother. Parsons' reports give many examples of this. On the whole, probably more men were affected by the disease than women, and this, like many other points, was the result of greater intercommunication.

As regards constitution, the statement that the robust, healthy individuals were chiefly attacked is confirmed by the age-curve given above.

The influence of occupation on the risk of infection depended simply on the liability of contact with infected individuals arising from that particular occupation. Many observers state that doctors furnished an exceptionally large contingent of influenza cases. But there are no statistics on the large scale to prove this.

When this question was discussed at the Medical Society in Cologne in 1890, after the epidemic it appeared that among 33 physicians present, 14 had had influenza, viz., 42.4 per cent., about the same as the general influenza morbidity of Cologne. The investigation, by Eichhorst, in Zürich, showed that among 50 doctors who were present at a meeting upon the first of February, 1890, 37, or 74 per cent., had had influenza.

A further example to those already produced is the following: A count was made in the Medical Society of Hamburg, as well as in Cologne and Zürich. Among the 108 physicians present at the meeting on February 11, 1890, 50 had influenza, while 58 remained exempt. So that in Hamburg, too, the percentage (46) is the same as that of the general influenza morbidity of this city.

Deep-sea fishermen and keepers in lighthouses and on lightships frequently have no communication with land for a long time. The careful official investigations which were made in England have shown that in 1889–1890, among 415 residents in the 51 lightships and in 20 lighthouses, upon the English coast, influenza occurred at only four places and affected only eight persons, and in every one of these cases direct communication with the infected coast could be definitely proved. Among the workmen upon the Northeast Sea canal only those were attacked who lived in Rendsburg. Those living outside in barracks were unaffected by the disease. The 438 lead miners of Rookhope, in a lonely valley in Durham, were quite exempt from influenza during the three epidemics (from 1889–1892).

The prevalent view at the beginning of the pandemic of 1889 of the miasmatic, that is to say, of the aërogenous nature and aërodromic transmission of influenza, raised, among others, the question whether those engaged in open-air occupations were earlier and more intensely attacked by influenza. Several of the older physicians (Bianchi, 1712, and others) were of this opinion. (The question itself is illogical, for the air from outside is continuously, although slowly, streaming through our rooms and dwellings, which are certainly not germ-proof.) On the contrary, the air in houses with influenza patients was probably far more laden with the air-borne germs than the air outside. Occasionally it seemed as if those whose occupations involved remaining for a long time in the open air, such as postal and railroad officials, and among these especially the traveling clerks, were early and severely affected by influenza. But in opposition to all these partly statistically proved statements, there are others from other places to show that residence in the open conferred a conspicuous immunity. Here statistics directly contradicted each other. Moreover, the well-arranged statistics regarding the incidence of influenza among the officials and servants of the various state railways shows that the personnel in the offices was oftener affected earlier and more severely than those on outdoor duty.

Quite a number of occupations were thought to confer immunity against influenza, so that workers in glass, coke, smelting ovens, chlorinated lime, petroleum, tobacco, cement, sulphuric acid, creolin factories, and tanneries were thought to be exceptionally exempt. But against all these statements others were brought which showed that these occupations did not confer immunity, so that we arrive at the following conclusion: Occupation and social positions have an influence on the disease incidence only in so far as certain occupations and conditions of life offer greater or lesser opportunity for intercommunication.

The differences occasionally noted in the frequency of the disease in different races of men, as, for instance, between natives and Europeans, depend undoubtedly upon other circumstances than race (communication, living, sanitation, etc.).

THE INFLUENCE OF METEOROLOGIC AND TELLURIC CONDITIONS.

In ancient times the thoughtful physicians who sought for the reasons and the nature of universal pestilences attributed to elementary powers, such as atmospheric and telluric conditions, an influence upon the entire population. Influenza especially, with its affection of the masses over large areas, fitted in with these ideas. History shows us the manifold variety and often extravagant nature of these hypotheses. The atmosphere was supposed to become foul, poisoned by the exhalations from the soil, etc. We cannot here enter into details concerning these theories, but the idea which the greatest of German philosophers, I. Kant, held in reference to the "noteworthy and wonderful influenza," of which he was a witness in the pandemic of 1782, is worth recounting. He, with his contemporaries, thought that "harmful insects" which were brought through Russian commerce to Europe gave rise to the disease, a conception which the "Medical Council" in Vienna at that time accepted. The authors who severely criticize these ideas should remember that the upholders of this view were decidedly nearer the truth than those who laid the blame of the pestilence on terrestrial magnetism, earthquakes, meteors, and volcanic eruptions, phlogistic air, electric fluctuations, and similar causes. Yet together with these speculations regarding the nature of the causation of the disease it is evident that most of the older authors recognized that influenza was quite independent of general atmospheric or telluric conditions of season, climate, site, etc., as shown by the writings of Salius Diversus (1536), Molineux (1693), and others. This independence has been proved in a high degree by our latest pandemic. In its hurricane course around the world it affected all latitudes and longitudes, all zones, having traversed all points of the compass from the northern polar circle to the equator; at one time in the hottest season, as in eastern central Africa, upon the Zambesi and Shiré, upon the Antilles and in the valley of the Indus; at another in the coldest season, as in Siberia and Greenland. The disease occurred in dry climates and seasons, as in northern Africa, Arabia, central Asia, and central Australia, while it flourished just as well as in the wet, tropical rainy season, *e. g.*, in India at the time of the southwest monsoon. In the same way it was independent of altitude, occurring upon the sea-coast as well as on the highest mountains. The disease was quite independent of wind and weather.

The weather reports of the meteorologic stations were studied with great industry in our latest pandemic. It was shown that during the epidemic of 1889 almost everywhere in Europe there were relatively high humidity, slight rainfall, and comparatively high temperature of the air. But it is in the highest degree unlikely that these meteorologic conditions had any influence on the rise and spread of influenza, or that they had the slightest influence upon the vitality of the free germs, or favored the public predisposition, yet upon these meteorologic conditions Assmann, Strahler, Ucke, Teissier, have formulated quite untenable theories.

Finally, as regards the influence of direction of the wind, the mode of distribution of influenza, quite apart from the meteorologic tables, shows the untenability of the general opinion that influenza was disseminated and carried by the wind from Russia. The prevailing wind was for the most part in a direction opposite to the course of influenza. No question has been more discussed by the historians of influenza than the mysterious direction of so many of the pandemics from east to west. The simple solution that this direction of the course of epidemics is the same as the direction of commerce between Russia, the home of influenza, and Europe, was not fully realized until our own time. If civilized states with similar commercial·intercourse had existed east of Russia, influenza in 1889 would have traveled with the same rapidity in the direction from west to east as it did from east to west.

But although the pandemics in their storm-like course around the world were independent of wind and weather, climate and season, it would, nevertheless, be a great mistake—and this mistake has generally been made even up to the present day—were we to conclude that the origin of the primary pandemics and the local epidemics which followed were entirely independent of season (see p. 552). The facts are as follows: 1. Nearly all the numerous pandemics which at various times have had their origin in Russia arose there in the late autumn or in the winter months. 2. The latest pandemic (1889) and the succeeding severe epidemics in Europe and North America, in the years 1891–1894, occurred almost exclusively in the cold season, the summer remaining conspicuously free.

The spread of the pandemic over the earth is entirely independent of all atmospheric or telluric conditions, and is exclusively the result of contagion. The origin of the primary epidemics and of the after-epidemics, however, is evidently dependent upon season.

A. Hirsch examined 125 independent epidemics or pandemics in reference to the influence of season, and found that 50 occurred in winter (December to February), 35 in spring (March to May), 16 in summer (June to August), and 24 in autumn (September to November). The conditions which make influenza dependent upon season cannot at present be defined. We must recognize that beyond the specific germ and its communicability by way of contagion, there are many conditions of whose influence we are still quite ignorant.

TRANSMISSION OF DISEASE THROUGH MERCHANDISE.

There exist many stories and reports to prove the transmission of influenza through merchandise of all kinds, letters, linen, clothing, fur, and even through grain from Russia. They date almost exclusively from the latest pandemic.

We shall mention only a few of these often-quoted examples: A celebrated case was the sudden outbreak of influenza in Paris at the end of November, 1889, among the employees of the Grands magasins du Louvre,—in one day, over 100 persons were taken ill, and in a few days the number rose to 500,—which it was sought to explain by the fact that imported merchandise from Russia had brought in the germs of the disease. But the exact inquiries of Brouardel and Proust proved the fallacy of this explanation. For three years no goods had been obtained from Russia.

Another frequently quoted example is illustrated by the case of the two winter porters upon the St. Gotthard Hospice in January, 1890. One of these had descended to the valley, to Airolo, at which place there was a marked epidemic. Returning to the hospice he remained well; his companion, however, ten days later, was attacked with symptoms which might have been due to influenza, but this is, at least, doubtful.

It is generally accepted that influenza was brought from the infected Louvre in Paris to Basel, through a shipment of merchandise. The first case in Basel is said to have been one of the workmen who was engaged in unpacking this consignment.

The fact that in many cities (Edinburgh, Vienna, New York, Boston, Rochester, London, etc.) the postal officials were the first persons to be affected, and that too in large numbers, has been used to support this idea, because they were the first to come in contact with infected material.

But although these, like many other examples in the literature, will not bear criticism, the possibility of communication of the disease by healthy persons and by merchandise, especially underwear, handkerchiefs, and, in the warm seasons, perhaps by flies and other insects, cannot be simply ignored.

The theory of transmission of the disease exclusively by traveling influenza patients and convalescents would have to be unduly stretched to explain the rapid transmission in the latest pandemic over so large an area in so short a time. The proof of the communicability of the virus by the healthy and by merchandise would considerably diminish these difficulties. We would also admit the aërodromic transmission of the germs to a certain extent through small distances from the place of an outbreak of the pestilence, to assist in explaining difficulties (explosive affection of the masses, compare p. 564) and in bringing them into accord with our contagionistic creed.

We feel unable to agree with the above-mentioned possibility that healthy individuals can carry about the germs in their nasal cavities and disseminate them without becoming infected, being themselves immune. We accept R. Pfeiffer's statement, that the specific bacilli have, up to the present, been found exclusively in influenza cases and convalescents.

The hypothesis of dissemination of the disease by merchandise has to meet the difficulty that the influenza bacilli, as R. Pfeiffer found, offer but slight resistance to drying. Moreover, no "permanent form" is known. It would not, however, be right to conclude that so permanent a form does not exist, or that conditions never arise outside the human organism and under natural circumstances (in contradistinction to artificial culture-media) to render it possible for the contagion to be preserved for some considerable time. Suffice it to say, we thoroughly agree with Pfeiffer's ideas regarding the transmission of influenza by merchandise, namely: (1) That "the dissemination of influenza by dried and pulverized sputum may take place to some small extent; (2) that the sputum of influenza patients if kept moist may preserve its infectious nature at least for fourteen days."

Only a very few authors have supported the view that influenza can be disseminated by drinking-water. The principal champion of this teaching, Teissier, although he has produced a number of remarkable facts concerning the dissemination of influenza in several Russian and French cities, nevertheless has signally failed to prove his hypothesis. The demonstration of R. Pfeiffer that influenza bacilli are quickly killed in drinking-water has destroyed the basis of this hypothesis.

IMMUNITY.

One attack of influenza in the majority of cases confers protection from the disease for some time, but the degree of immunity does not approach that conferred by small-pox, whooping-cough, scarlet fever, measles, or enteric fever. Certainly, during the short, eight-week epidemic of 1889–1890, a second attack was a rare occurrence. But from the later epidemics it became evident that this immunity was merely a question of time. Cases of recurring attacks of the disease occurred in one and the same individual, and even in the same family at different times, and were common enough in the last influenza period. Some authorities greatly overestimate this immunity. For instance, Bäumler thinks that the aged, who in the last pandemic showed such extraordinarily slight morbidity, still retained the immunity conferred upon them by passing through an attack of influenza in the epidemic years of 1837, 1847, and 1857. Regarding this, Ed. Gray mentions already in 1782 that "it was also remarked that many persons who escaped the epidemic of 1775 were affected by that of 1782, and many who escaped the latter were affected by the former" (E. S. Thompson, p. 110).

Several physicians, especially many English and French, as Teissier, Squire, Joy, and others,* believe that one attack of influenza actually predisposes to further attacks. A. Gottstein considers this increased predisposition to be an explanation of influenza becoming endemic, whereas we believe that the growing immunity of the population accounts for the successive decrease in the morbidity of the later epidemics. (See p. 549.)

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* See Parson's report.

This apparent contradiction becomes intelligible when we distinguish clearly between relapses and new infections. Relapses are the rule in influenza. "La grippe est une maladie à rechutes." Relapses occur frequently even after the patient has been up and about or has left the house for the first time, and are usually ushered in by some complication or sequela. No doubt many writers have erroneously termed these late relapses new infections, and have based upon them their opinion of "increased predisposition."

On the other hand, those cases should not be counted as relapses in which a convalescent influenza patient, after two or more weeks, has a rigor and passes through a second typical attack of influenza. The attempt to discard such unquestionable reinfections by the supposition that the first or the second attack might have been an ordinary coryza, is an explanation which cannot be maintained against the actual facts.

The question asked in the German collective investigations, "How often have you seen the relapses?" was in itself so ambiguous that a direct answer could not be expected. Of the observers, 10 per cent. saw no relapses, 63 per cent. saw them but rarely, and 23 per cent. frequently.

Of greater value are the following statistics: Turney, at St. Thomas's Hospital in London, found that 5 per cent. of the influenza patients admitted in the spring of 1891 had had influenza during 1889–90. Dickson found that those custom and postal officials of London who had had influenza during 1889–1890 furnished but half as large a contingent in the second epidemic as those who had remained unattacked in the first epidemic (5 to 10 per cent.). In the epidemic of 1891–1892, of 272 influenza patients admitted to the Urban Hospital (Berlin), 8 per cent. had had influenza during 1889–1890; of 105 pupils in the seminary at Preisketschan, 32 per cent.; while of 122 influenza patients in the seminary at Waldenburg (Saxony), 35 per cent.; of 905 patients in Lübeck, 24 per cent., and of the private patients of Caldwell-Smith, 25 per cent., had been attacked by the disease during the epidemic of 1889–1890. In the industrial school at Swinton (Manchester), which was cut off from communication, 171 children out of 589 had influenza during the first epidemic. Of these 171 children, 2.6 per cent. became affected for the second time in 1891, while of those who had remained exempt in the first epidemic, 5.7 per cent. contracted influenza during the second epidemic.

In addition to the acquired immunity there is also a congenital or natural one. Infants to some extent possess such an immunity. But many adults, for instance, physicians and nurses, who were in constant contact with influenza patients, remained exempt from the disease during all the epidemics. In other cases this form of immunity is only a temporary one. Many physicians who escaped during the first epidemic had to pay their tribute to the disease during later epidemics.

DURATION OF PERIOD OF INCUBATION.

At the beginning of the pandemic of 1889, by reason of the sudden affection of the masses, the assertion was often made that influenza had no period of incubation; that we had to deal with a miasmatically distributed toxic substance, which, immediately on entering the human organism, displayed its morbific character. At the present time we need mention this theory only to reject it, although it was then held by many leading medical authorities.

No doubt the time elapsing between the inception of the germs, viz., the moment of infection and the moment at which symptoms appear, is short—in the greater number of instances it is from one to three days. But numerous observations are recorded, even from the earlier epidemics, which make it probable that the period of incubation may be as short as twelve hours. The duration of the period of incubation, according to the English collective investigation, may be taken, from the concordant answers of the majority of observers, to be from one to three days (Parsons' reports).

BACTERIOLOGY OF INFLUENZA.

The rapid distribution of the pandemic immediately led the bacteriologists of all countries to investigate and try to discover with the microscope the new germ, the specific cause of the disease. There was a veritable plethora of reports produced regarding the bacteriologic findings in the various secretions of influenza patients, especially in the pneumonic and pleuritic exudates. In every case it was previously well-known pathogenic cocci (streptococci, staphylococci, pneumococci, occasionally also Friedländer's bacillus) which were found, either singly in pure culture or in combination with each other.

In some places, as Vienna, Strassburg, etc., it was principally the Diplococcus lanceolatus which was found in the pneumonic areas, in the sputum, and in the otitic and meningeal pus, while in other places, like Bonn, Paris, etc., streptococci were usually found. All the expert bacteriologists correctly interpreted their findings at that time in considering the above-named cocci as of only secondary significance. Only one observer was so far misled by the frequent presence of the streptococci as to believe himself justified in proclaiming the Streptococcus pyogenes as "the most probable exciting cause of influenza." This attempt to identify the *causa morbi*, based chiefly upon the presence of streptococci in the inflamed lungs of influenza patients, is all the more incomprehensible since long before the outbreak of influenza it was well known that streptococci were frequently found in the mixed infections of various forms of, and particularly of croupous, pneumonia (Naunyn, 1887), but also that these organisms probably possessed the power in themselves of causing pulmonary inflammation.

The historic micrococci which O. Seifert first found in a small "influenza" epidemic of 1883, judging by description, were probably streptococci. Some observers who found previously known pyogenic cocci, nevertheless wanted to consider them, on account of unimportant tinctorial or cultural peculiarities, as a variety peculiar to influenza. But all these observations, as well as those of a few "specific varieties of bacteria" claimed to have been found at that time, some being cocci, others bacilli or diplobacilli (Teissier), and even some flagellata, proved to be fallacious or without significance. Thus, the very promising bacteriologic investigations of influenza during the years 1889–1892 produced completely negative results, but the energy applied to the investigations was not wasted, since the results showed that in the various pathologic conditions produced by influenza, especially in the pneumonic and pleuritic exudates, simultaneous or secondary infection by the well-known pyogenic and pneumonia-producing agents plays an important rôle.

The hope of finding the specific cause of influenza appears to have been universally abandoned, when R. Pfeiffer, in the beginning of the year 1892, published his sensational announcement "regarding the cause of influenza," a discovery which found recognition and substantiation by the bacteriologists of all countries. In the following description of the most important characteristics of the influenza bacillus we adhere strictly to the account given by its discoverer.

Morphology.—The influenza bacilli are extremely small rods, being among the smallest ones that have yet been cultivated. They are only two or three times as long as they are broad [being 0.4 μ

broad and 1.2 μ long.—ED.]; longer forms are occasionally met with in sputum, and more frequently in pure cultures; these are to be regarded as short pseudostreptothrix forms. The ends of the rods are rounded. They have no capsules. They are non-motile in hanging drop. They do not stain by Gram's method. The size of the bacilli in sputum sometimes varies considerably, just as many other kinds of bacteria do.

The accompanying photomicrograph represents the sputum from a recent febrile case, and is taken from the article of R. Pfeiffer.*

Very frequently two extremely short bacilli are found together, one closely behind the other. Weak staining will sometimes give the appearance of a vacuole in the center of the bacillus, produced by a deeper polar staining. In this way preparations remarkably like diplococci may be produced. Doubtlessly these small, numerous influenza bacilli were seen by many observers, even in the first pandemic of 1889-1890, as indicated in several descriptions (Babes and others). Pfeiffer, in particular, had seen them already in 1890, and had published photographs of the same in M. Kirchner's article.

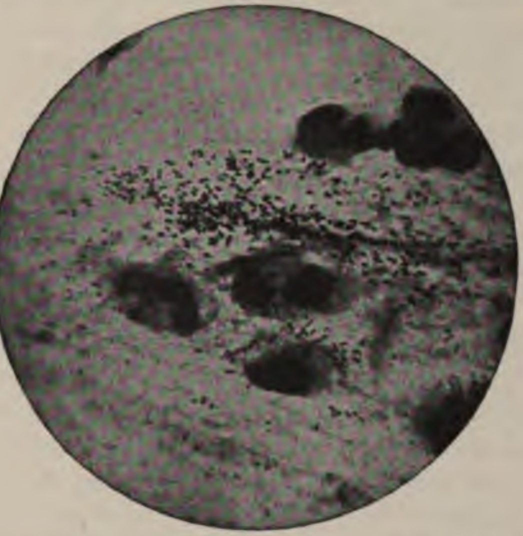

FIG. 39.—INFLUENZA BACILLI IN SPUTUM (according to R. Pfeiffer; photomicrograph, × 1000).

In recent, still febrile cases of influenza the bacilli are found in heaps or in clumps embedded free in the mucus of the sputum, while the pus-corpuscles contain but few bacteria. During the course of the disease and during convalescence the microscopic picture changes in a characteristic manner. The number of the free organisms gradually decreases, but the pus-cells are crowded with the fine rods. During this stage involution forms are frequently seen; the bacilli become abnormally narrow or plump, assume irregular shapes, stain badly, and become converted into a fine molecular detritus. Bacteria undergoing such changes are found, upon inoculation into culture-media, to be dead.

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* "Zeitschr. f. Hyg. u. Infectionskrankh.," vol. xiii, Fasc. 3, Plate IV, Fig. 1.

The period during which influenza bacilli are present in the sputum cannot be definitely stated. In typical acute cases they are present only for a few days. [The period has become gradually less since the epidemic of 1890.—Ed.] In those cases where convalescents recover very slowly and suffer for weeks with bronchial manifestations, the specific bacilli are found for weeks in the sputum, which indicates that "local influenza areas" continue to exist in isolated bronchial areas. Pfeiffer describes these cases as "chronic influenza." Especially in phthisical individuals affected by influenza, and particularly those with cavities, influenza bacilli may be found in the sputum for weeks and even months (Pfeiffer, Kruse).

Staining of the Influenza Bacilli.—The influenza bacilli take the basic anilin stains very badly, and belong to the class of microbes which stain with difficulty. It is necessary to allow the dried and fixed cover-glass preparations of sputum to remain floating for some time—at least ten minutes—upon the staining solution. It was no doubt partly through neglect of this precaution that the influenza bacillus which presents so characteristic a picture of a pure culture in sputum was so long overlooked. The best stain is Ziehl's carbol-fuchsin solution diluted 20 times, or hot Loeffler's methylene-blue solution. [Bacillus influenzæ stains more deeply than the other bacteria present.—Ed.]

Cultivation of Influenza Bacilli.—The obtaining of a pure culture and the further cultivation of the influenza bacilli upon artificial culture-media at first offered great difficulties. The ordinary culture-media all proved to be insufficient. Although Pfeiffer occasionally and exceptionally succeeded in cultivating one generation of the bacilli upon ordinary agar at incubator temperature, and although Kitasato states that he succeeded in obtaining several generations upon glycerin-agar, nevertheless these culture-media must be considered as inadequate and only occasionally sufficient.

Subsequently Pfeiffer, after "innumerable futile attempts," found a suitable culture-medium for easily and certainly cultivating the influenza bacilli, in agar streaked with sterile blood. The procedure is as follows:

> The surface of a slanting agar tube or the surface of agar in a Petri dish is streaked with blood obtained under aseptic precautions, most conveniently blood from the finger-tip. All varieties of blood are efficacious, but the cultivation upon agar streaked with blood obtained from the pigeon is characterized by a particularly rapid and luxurious growth (Pfeiffer).
>
> The prepared blood-agar tubes are provided before use with rubber caps, and are placed for twenty-four hours in the incubator. It is a fundamental rule, as far as the sputum is concerned, to use only fresh bronchial secretion obtained in sterile dry receptacles.
>
> R. Pfeiffer's method for the obtaining of pure cultures is as follows: "Bronchial sputum or fluid from lung areas infiltrated with pneumonic exudate is rubbed up with one to two cubic centimeters of bouillon (sterile normal salt solution may also be employed) until an evenly distributed, only slightly turbid emulsion is produced. Loopfuls of this emulsion are transferred to blood-agar and controls also on common agar or glycerin-agar. The emulsion should be evenly distributed upon the surface. The test-tubes are now placed in the incubator (37° C.). After twenty to twenty-four hours the influenza colonies are seen on the blood-agar, looking like fine drops of dew which, microscopically, are seen to be made up of fine rods. The control test-tubes will have remained either sterile or contain only isolated colonies of other forms of bacteria, usually streptococci or Frankel's diplococci."
>
> W. Kruse describes a "brush method." Several tubes containing 2 per cent. agar, after pouring off the condensation water, are melted, and while hot poured into Petri dishes. These are allowed to cool uncovered under glass shade, to prevent the subsequent formation of condensation water. Then, with an ordinary paint-brush which has been sterilized in steam, pigeon blood is brushed over the surface of the agar plate. In the same way, also with a brush, the material to be examined for influenza bacilli is distributed over the surface, either direct or after dilution in sterile bouillon. From the finished plate, with a new brush, some of the material may be taken off and placed upon a second blood-agar plate, etc. In this way any dilution required may be obtained. [Symbiosis, especially with Staphylococcus aureus, favors the cultivation of Bacillus influenzæ (Grassberger and others). A simple, good nutritive medium can be made by boiling up blood, without the serum, with normal NaOH, adding this to liquefied agar, and shaking thoroughly. The medium remains efficient and reliable for a long time (Ghon and Preyss).—Ed.]

The influenza colonies growing upon blood-agar are so characteristic that they are easily recognized among several hundred other colonies of bacteria. They usually occur as clear, limpid droplets lying close together, with only a slight tendency to coalesce. Usually the colonies are so small that a hand-lens is necessary to see them clearly. With only a few and widely separated germs, from which the colonies can readily expand, they often attain considerable size

—about the diameter of a small pin's head; but even these, the largest colonies, show a characteristic glassy transparency. We may further mention the following cultural characteristics of influenza bacilli: 1. They are strict aërobes. 2. They grow only at blood temperature (37° C.)—the maximum temperature limit 42°, and the minimum, 28° C.; at room temperature, from 23° to 24°, there is not a sign of development even after four days. 3. Their period of viability in bouillon is considerable under ordinary circumstances; they do not die off until from fourteen to eighteen days. For the same period of time, and sometimes even for twenty days, they retain their vitality on blood-agar. On this medium it is immaterial whether the developed cultures remain in the incubator or are kept at room temperature. Nevertheless it is well to make subcultures every four or five days. 4. The blood-agar cultures in the incubator are fully developed in from twenty to twenty-four hours. 5. A persistent form, spores, have not yet been demonstrated. 6. In drinking-water the bacilli very rapidly lose their vitality in from twenty-four to thirty-six hours. 7. In sputum that has been kept moist the saprophytes which are present soon overgrow the influenza bacilli, though, according to Pfeiffer, they retain their infectiousness in moist sputum at least for fourteen days. 8. The influenza bacilli are conspicuously sensitive to drying. Blood-agar cultures which have been streaked upon glass plates and have been dried at a temperature of 37° C. become sterile in from one to two hours; dried at room temperature, in from eight to twenty hours. Sputum from grip patients dried at the ordinary room temperature was sterile in from thirty-six to forty hours.

True influenza bacilli, according to Pfeiffer, are found exclusively in endemic and epidemic influenza. In the secretions of an ordinary coryza influenza bacilli are never found. E. Neisser found them once in the sputum of a phthisical patient who, although not affected by influenza himself, was in a bed in the same ward with influenza patients.

In the bacteriologic diagnosis of influenza we must remember that, unfortunately, there exists also the pseudo-influenza bacillus. In three cases of diphtheric bronchopneumonia Pfeiffer found in the smear preparations "numerous fine rods which, from their form and staining properties, could hardly be distinguished from the influenza bacilli, which they resembled also culturally, since they grew only upon blood-agar and formed colonies which resembled the influenza colonies in the minutest details." For the extremely subtle points of difference between these confusing "pseudo-influenza bacilli" and the "genuine" ones we must refer our readers to the original treatise.*

Opinions differ regarding the presence of influenza bacilli in the blood. Canon asserts that he found them in the blood taken from the fingers of 20 patients "in nearly all cases"; Klein (London) found them only 6 times among 43 fresh cases; Pfuhl, in several cases, also obtained positive results. [According to Jehle, the bacilli appear in the circulation particularly in the cases where influenza occurs as a secondary infection to one of the exanthemata. His observations were made on the heart-blood after death. Slawyk records the case of a child of nine months, in which he found the bacillus in the circulation a few hours before death.—Ed.] On the other hand, Pfeiffer and Beck never found the bacilli in the blood, either microscopically or in cultures. Pfeiffer, however, twice saw isolated influenza bacilli in the veins in microscopic sections, and he was able several times to cultivate a few colonies from the spleen and kidneys.

The fact that the influenza bacilli are but rarely found in the blood does not prove that they do not enter the circulation. It is the same with influenza bacilli as with many other micro-organisms whose demonstration in the blood has either been unsuccessful or has succeeded only occasionally. The numerous organic lesions (inflammations) point to the transportation of the suspected microbes by the blood, and the actual discovery of the specific bacillus in the affected areas demonstrates its etiologic significance. On the other hand, the presence of influenza bacilli in the tissues of various organs has not been satisfactorily proved.

Pfeiffer found crowds of the bacilli under the pulmonary epithelium in patients suffering from influenza pneumonia, but only very few in the submucous connective tissue. A. Pfuhl found the small rods in several cases of influenza encephalitis, partly in the membranes and partly in the substance and fluids of the central nervous system, but always within the blood-vessels or perivascular lymphatics. He also found them in areas of softening of the brain and spinal cord; in a cerebellar abscess; both microscopically and culturally in an area of softening in the cerebellum; in the blood, and in the aqueous humor; in smear preparations from the liver, spleen, and kidneys; in sections of the brain in whose capillaries they were found both isolated and forming quite extensive thrombi; and, finally, in sections from the liver, partly within the capillaries, partly free in the tissues, and in accumulations of detritus. A further contribution to this question is that of Nauwerck, who, in a case of influenza encephalitis, found micro-organisms similar to Pfeiffer's bacilli in sections of the cerebellum, which was the organ chiefly affected, in the apoplectic areas of the cerebellum, in the adjoining hemorrhagic area of softening, in the perivascular lymph-spaces, but not in the blood-vessels. The cultures, too, resembled and were probably identical with those of the influenza organism.

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* "Zeitschr. f. Hyg. u. Infectionskrankh.," Bd. xiii, S. 383.

Experiments on Animals.—All attempts to produce typical influenza in animals by inoculation, either of richly infected sputum or of pure cultures of influenza bacilli, have failed. In particular it has been impossible to demonstrate any increase of the inoculated influenza bacilli in the body of the animal [except when injected intraperitoneally.—Ed.]. Pfeiffer, it is true, succeeded in causing general and local symptoms of the disease in monkeys (namely, fever, and once, by intratracheal inoculation, a retrotracheal abscess with purulent bronchitis, in which a few dead influenza bacilli were found. By giving large doses he was able to kill monkeys and rabbits which manifested severe "symptoms of poisoning" due to the intoxication caused by the simultaneous inoculation of "influenza toxin" with the bacilli. [This occurred even when killed cultures were used. The symptoms (dyspnea and muscular weakness) bore sufficient resemblance to those in man for justifying the deduction that the influenza toxin is chiefly concerned in this production. In animals, inflammatory conditions can be produced by painting mucous membranes, especially if injured, with cultures, and particularly in the osseous system after injury, also otitis media. The bacillus can be recovered from the lesions (Perez). Repeated injections of toxins do not lead to the production of an antitoxic or bacterial serum, and the animals used will succumb to a larger dose of culture.—Ed.]

Klein (London) made inoculation experiments with influenza sputum containing many bacilli, and also with pure cultures of the organisms, upon 24 monkeys, by means of subcutaneous and intratracheal inoculation; the results were consistently negative. Only in one monkey which died of pneumonia were Pfeiffer's bacilli found, as well as other microbes.

The best proof of the immunity of monkeys toward human influenza seems to me to be afforded by the fact that these animals in the monkey-house of the zoölogic gardens in London showed no signs of the disease, although in the influenza period they were visited by thousands of persons and must certainly have been coughed at by innumerable ambulatory influenza patients. It will be appropriate to consider here the much-discussed controversial question of influenza of domestic animals.

"INFLUENZA" OF DOMESTIC ANIMALS.

The statement that domestic animals, especially horses, are simultaneously affected with man at the time of large influenza epidemics, and are victims of this human disease, can be traced back for some distance in the annals of epidemics. In England especially, both during the previous century as well as during all the epidemics of the present century, was this point the subject of special attention. In the last pandemics, too, attention was drawn by Finkler and others to the "highly astonishing" and "interesting" coincidence of human influenza and that of horses.

The English collective investigation of 1889–1890 laid such importance upon this point that on their inquiry forms a separate question was given to it: "Have you observed any unusual complaints among domestic animals? in what animals and with what symptoms?"

The answers were very numerous (compare Parsons' reports), and were affirmative in regard to horses, but negative regarding cats, dogs, and canaries and other domestic birds.

Although there is a considerable literature on this subject, it can really be dismissed in the following few words: Human influenza is a disease which is peculiar to the human race and, up to the present time, has not been observed in animals.

This statement applies also to the much-discussed influenza of horses, an epizoötic disease which is quite common and was not more prevalent at the time of the last influenza epidemic than before. Various contagious diseases of the horse are called "influenza."

1. The catarrhal influenza or "la grippe," a disease of the whole respiratory mucous membrane, occasionally ending in bronchopneumonia.
2. The "erysipelatous influenza" (erysipelas, "horse typhoid," horse scourge), characterized by a marked involvement of the digestive tract, by petechiæ, erysipelatous swellings, conjunctivitis ("pink eye"), grave nervous symptoms, but comparatively benign. It is alleged that this form is transmissible to dogs and to human beings.
3. The "pectoral influenza," a contagious pleuropneumonia due to a diplococcus, which differs, however, from the Diplococcus pneumoniæ of man, and causes, when inoculated into mice, fatal septicemia. Of these forms it is only the first, the catarrhal, which has slight symptomatic resemblance to, but has really no connection with, human influenza, for the equine affection has frequently raged at times when the human race was entirely free from influenza.

ENTRANCE AND EXIT OF THE INFLUENZA ORGANISM.

In the majority of cases, undoubtedly, the influenza germ enters and settles in the respiratory tract, generally in the upper, nasal, or nasopharyngeal portion, but occasionally also primarily in the trachea, bronchi, or even the alveoli, as shown clinically by the occurrence of a primary influenza pneumonia.

The respiratory tract is probably also the only exit for the bacteria, at least so far as the danger of infection is concerned.

The exclusively gastro-intestinal forms of influenza indicate a possible primary invasion of the germ by the stomach and intestinal canal, but it is very likely that in this case also the primary entrance is by the upper respiratory passages, although without any noticeable lesion at the point of entrance. This also is the probable explanation for the frequent purely nervous forms of influenza—that is, of those which run their course without any appreciable respiratory or gastric manifestations.

From the facts just mentioned, certain conclusions logically follow regarding the most important mode of transmission of the contagion. There can be no doubt that a disease which affects the respiratory passages, and particularly the upper portions, in such a striking way, must be air-borne, just as the germs of the intestinal infectious diseases, cholera, typhoid, and dysentery, enter principally by the "ingesta" (water and food). While holding this view, we are far from admitting the erroneous miasmatic theory of the panaërodromic distribution of influenza from Russia over the whole earth. At the point of outbreak of influenza the aërodromic convection of the contagion doubtlessly plays an important and even a decisive part. The sensitiveness of the influenza bacilli to drying, which has been proved bacteriologically and is a preliminary condition for the formation of dust, does not disprove this, nor does the aërodromic distribution of the influenza germs in the least affect our belief in the contagionistic theory, which recognizes, at present at any rate, a multiplication of the micro-organisms only within the human body.

RELATION OF INFLUENZA TO OTHER INFECTIOUS DISEASES.

It is not our intention to enter into the controversy regarding the epidemiologic relation of influenza to other infectious diseases (especially scarlet fever, measles, typhus, diphtheria). It will suffice to quote the opinion which P. Friedrich, after an exhaustive study of the literature on the subject, has formed. He says: "From the sum-total of the observations it can be deduced with certainty that there was no mutual correlation between influenza and other infectious diseases during the epidemic of 1889–1890." Wutzdorff arrived at similar negative conclusions regarding the after-epidemics, and so did A. Ripperger, in his "historic-pathologic studies" concerning the subject under discussion.* Nevertheless, the general rule that during the existence of great pestilences the other acute infectious diseases remained in the background probably held good also at the time of the influenza pandemic.

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* "Münch. med. Wochenschr.," 1893, No. 41.

PATHOLOGY AND TREATMENT OF INFLUENZA.

THE GENERAL FEATURES OF THE DISEASE AND ITS DIFFERENT VARIETIES.

The clinical picture of influenza is so varying, so "protean," as it is termed, that many authors have expressed the opinion that there is no typical form of influenza—"Every case presents a different picture," or, "But few cases are alike in every respect." Such statements are gross exaggerations. It is, however, true that no acute infectious disease shows such a variety of different groupings of the various symptoms or variety of complications and sequels as does influenza. Nevertheless, a few quite characteristic types can be described to which the large majority of the cases conforms.

The typical influenza consists in a sudden pyrexia of from one to several days' duration, commencing with a rigor, and accompanied by severe headache, generally frontal, with pains in the back and limbs, by prostration quite out of proportion to the other symptoms, and marked loss of appetite.

To these characteristic symptoms may be added, in most cases, as might have been expected from our knowledge of the organs to which the influenza germs first gain access, catarrhal phenomena affecting the respiratory tract, particularly the upper parts (coryza), and occasionally the lower parts—the trachea and the bronchi. These catarrhal phenomena occur so frequently that they must be regarded as belonging to a typical attack of influenza.

This general class is subdivided into groups which are characterized, apart from the fever which is common to them all, by the predominance of either the nervous, the catarrhal, or the gastric symptoms. A fourth class combines several or all of these typical influenza symptoms: Fever, nervous, respiratory, and gastric phenomena. The ancient division of influenza into nervous, respiratory, and gastric forms was retained in the last pandemic. But this classification is insufficient, for the numerous mixed varieties find no place in it, and, what is more important, neither do those innumerable cases in which the influenza arises as a simple pyrexial attack of short duration, without special nervous and gastric symptoms and without any respiratory symptoms. [In young children (four to twenty-four months old) the attack commences, according to O'Donovan, with prodromal excitement, activity, and unrest. Pyrexia and vomiting follow, the latter not stopping until inhibited by a laxative. The tongue is clean; pulse, 160 to 180; urine, markedly yellow.—Ed.] Below we give a purely pathogenetic classification, which has several advantages over a purely morphologic division. We differentiate:

1. **The Purely Toxic Varieties.**—To these belong:

(1) The *simple influenza fever*, those mild cases where, apart from a rise in temperature and the general malaise, which depends upon the fever (headache, weakness, anorexia), specific influenza symptoms, especially all inflammatory processes, are absent. In such cases we have merely the effects of the influenza toxin. The physicians of the last century already recognized an influenza without catarrhal symptoms. Gray writes in 1782: "In some the catarrhal symptoms were entirely wanting, the disorder in those cases being like a common fever." More recently Norman Kerr, Rosenbach, Bäumler, and others have drawn attention to this "simple influenza fever." Thomas and Obkircher believe that it is especially frequent in children.

(2) The *nervous form of influenza*, those cases in which, as well as fever, but quite in disproportion to its height, marked nervous signs, such as headache, pains in the back, limbs, and joints, general nervous prostration, neuralgia, insomnia, are the principal symptoms, while inflammatory changes in the respiratory and digestive tract are absent. Here, again, we have a simple toxic action affecting especially the cerebrospinal system.

2. **The toxic inflammatory** varieties of influenza, in which, in addition to the above-mentioned toxic phenomena (fever, nervous symptoms), inflammatory changes play a principal part. To this variety belong two principal groups:

(1) The *catarrhal-respiratory influenza*, characterized by coryza, laryngeal-tracheal, and bronchial catarrh.

(2) The *gastro-intestinal* variety, characterized by catarrhal processes in the gastro-intestinal mucous membrane, with heavily coated tongue, complete anorexia, vomiting, and diarrhea. This variety is much more uncommon than any of the previously mentioned forms.

Too much stress cannot be laid on the fact that typical influenza very frequently—perhaps in one-quarter of the cases—may occur without any symptoms referable to the respiratory tract. Before the outbreak of the last pandemic probably every physician would have considered an inflammatory catarrhal condition of the respiratory mucous membrane, especially a severe coryza and bronchial catarrh, as essential to the clinical picture of influenza. On account of the numerous cases at the commencement of the pandemic of 1889 without coryza and bronchitis, some physicians considered that the arising epidemic could not be influenza. In Paris it was thought more probable that the condition was dengue ("dengue atténuée"), since in this disease catarrhal symptoms of the respiratory tract are entirely absent.

The forms just described constitute the principal varieties of influenza, and include the great majority of influenza cases. They represent simple uncomplicated influenza.

This picture of the disease may be confused either by the predominance of some of the typical symptoms, or by the occurrence of other complications. Thus there may be, in the febrile form, hyperpyrexia or long-continued fever, with a dry tongue and sordes on the teeth; or in the nervous variety, delirium, coma, and meningeal symptoms; or in the respiratory influenza, capillary bronchitis, pneumonia, pleurisy, etc.; or in the gastro-intestinal variety, meteorism, severe colic, profuse and even bloody diarrhea, and peritoneal symptoms.

By a combination of several of these complications the disease may simulate septicemia, acute miliary tuberculosis, and very often enteric fever (the "typhoid form" of influenza). We have not, however, come across any case in which we were long in doubt regarding the diagnosis between enteric fever and influenza. The sudden onset with rigors is peculiar to influenza; and so rare in enteric fever that from this fact alone—to mention only one of the many differential signs—a definite diagnosis can be made. In addition to the varieties mentioned, other types have been described, without, however, bringing the purposed order into the chaos of complicated forms of influenza. The rare "forme cardiaque" of Huchard may be mentioned, in which, early in the acme of the attack in sthenic, robust individuals, alarming signs of weakness appear (in so-called syncopal forms of the older authors) in consequence of the unusually intense action of the influenza toxin on the heart. We shall return to some of the important symptoms, in particular to the complications and sequelæ of influenza, in our description of the lesions of the various organs.

We may point out here that: (1) The frequency of the several clinical varieties; (2) the numerical relation of the simple to the complicated cases; (3) the frequency of special complications varied considerably at different times and at different places. The reports from all countries show this to be the case. It will suffice to emphasize the following important fact, that the simple, typical, uncomplicated influenza which occurred so frequently in the pandemic of 1889–1890 was less frequent both absolutely and relatively in the later epidemics, while the complicated cases were much more frequent. This agrees with the ascertained greater mortality of later epidemics, to which we have already called attention. (See p. 550.)

We cannot here go into a comparison of the frequency of the clinical course of influenza in former epidemics with that of our latest pandemic. We should encounter, in doing so, considerable differences, sometimes so great that doubt might arise whether some of the former epidemics really were influenza. A study of the tabulated arrangement of the principal symptoms of influenza in the epidemics from 1510 to 1889 by E. Symes Thompson (*loc. cit.*, p. 467) is very instructive.

ONSET AND DURATION OF INFLUENZA. CONVALESCENCE. RELAPSES.

The onset of influenza is almost always sudden, hence the early German name, "Blitzkatarrh."* The disease begins with a chill, frequently with a rigor; simultaneously with this the temperature rises. Only in rare cases—according to our own statistics† only in 7 per cent.—were there any prodromal symptoms of one or more days' duration, such as general malaise, debility, or coryza. Only in the mildest rudimentary form is the initial chill absent. Such cases are often indistinguishable from a simple coryza, diffuse muscular rheumatism, cephalic neuralgia, migraine, or a mild bronchial catarrh.

In some rare but very remarkable cases influenza begins suddenly, with quite abnormal symptoms. The disease may be ushered in by a deep faint, by convulsions, especially in children, by a fall with epileptiform convulsions and coma of long duration, or by a sudden terrible sensation of vertigo, on which stupor and lethargy may follow. But an influenza commencing with such alarming symptoms may run a mild, rapidly convalescing course. This occurred in one of the cases described by us, which was brought into the hospital with a diagnosis of apoplexy. At that time there was no pyrexia, but on the following day the fever was high and the usual symptoms of influenza were present. Consciousness returned at the same time, and after three days the patient was fully convalescent. As in all acute infectious diseases (enteric fever, pneumonia, etc.), so occasionally with influenza, it happens that the disease commences with the symptoms of an acute psychosis, and, what is of special importance, without at this period any rise of temperature. The varieties of this initial delirium and initial psychosis are very manifold. We may mention: Stupor, sensations of fear with hallucinations, confusion, maniacal excitement with exaltation and restlessness, or even acute mania. Such cases were occasionally brought into the hospital with the diagnosis of acute mania, and thence, unfortunately, since there was no fever, sent to an asylum, from which, after passing through an attack of influenza, they were discharged cured a few days later. Occasionally, in alcoholic patients, the onset of influenza took the form of severe delirium tremens. We shall revert to this later. The explanation of these fulminating initial symptoms with severe nervous phenomena is obvious. They can be due to nothing else but an acute intoxication from the influenza toxins entering the circulation and affecting primarily the cerebrum.

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* See p. 552.

† Collective Report of Cologne, 1890, *loc. cit.*, p. 25.

Here, too, we may briefly allude to those exceedingly rare modes of onset of influenza in which, as cases coming under our own notice and others mentioned in literature* have shown, the disease may arise suddenly with severe gastro-intestinal symptoms, with continuous vomiting, colic, and diarrhea, so that the case seems to be one of acute poisoning. In one of our cases all the symptoms pointed to a perforation of the appendix; the abdomen, as occasionally occurs at the onset, was of a board-like hardness, and exceedingly tender to the slightest touch. On the third day, however, the abdominal symptoms disappeared and influenza, with all its typical symptoms, was revealed, with the later addition of pneumonia.

The duration of an attack of simple uncomplicated influenza, whatever its special clinical variety, is short—in the great majority of cases, only one or a few days.

We may confirm this universal experience, although it is hardly necessary to do so, by some quotations from statistics. Peacock reports that in the epidemic of 1847–1848 the duration of the disease among the London police averaged about three days; only in 1 per cent. of the cases was the duration over a week. In 45,100 grip patients treated in the Prussian army during 1889–1890, the average duration of the disease was five days. Among the 2415 school-children of the district of Waldkirch (Baden), the duration of the disease was "accurately" ascertained, and in 15 per cent. of the cases it was one day; in 63 per cent., two to five days; in 16 per cent., six to ten days, and only in 4 per cent. of the cases was the duration longer than ten days. Among 192 influenza patients of the prison of Münster, 41 per cent. were so slightly affected that it was not necessary for them to cease working; 34 per cent. were ill two to three days; 15 per cent., four to seven days, and 10 per cent., longer than a week. Of the 137 influenza patients of the reformatory of Münster, 70 per cent. could continue their work; 11 per cent. were ill one to three days; 10 per cent., four to seven days; and only in 9 per cent. of the cases was the duration of the disease longer than a week. Numerous similar statistics might be quoted. If we now give the statistics of the Berlin "sick-clubs," which do not agree with those just mentioned, we do it mainly to prove the justice of our previous criticism of the morbidity of the "sick-clubs." (See p. 566.) The results obtained by the Bureau of Vital Statistics of the city of Berlin from data supplied by the clubs, etc., show that the duration of the disease in 1 per cent. of the cases was one day; 31 per cent. of the cases, seven days; 31 per cent., fourteen days; 16 per cent., three weeks; and 20 per cent. were ill more than three weeks. The inference may be drawn from this that an enormous number of the mild cases was not recorded at all, to which point we have already called attention under Morbidity. (See p. 566.) Such statistics have much less value than those depending on estimates made by the doctors.

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* Compare Friedrich, *loc. cit.*, p. 331.

Convalescence.—In most cases the patient is able, in a short time, to resume his usual occupation. But frequently even the mildest cases and the most simple attacks of influenza are followed by a long and tedious convalescence, complicated either by an obstinate neuralgia or an indescribable weakness and debility, by loss of energy, both bodily and mental, by depression, insomnia, or by prolonged and persistent gastric disturbances and anorexia. This difficult convalescence is usually far worse for the patient than the brief attack of influenza.

Relapses.—We pointed out, in the section on Immunity (see p. 577), the frequency of relapses in influenza. These relapses generally occur in the following way: One or more days after the fever has disappeared and the patient feels himself convalescent in every other respect, febrile symptoms appear anew, either gradually or suddenly, accompanied by chills, and the symptoms of the initial influenza recur (repetition of the first attack). But the relapse may also develop additional symptoms. If the first attack was only nervous, the relapse may include also catarrhal respiratory symptoms. The contrary condition—that is, respiratory symptoms first and nervous symptoms later—is much rarer. The second attack is often more severe than the first; very frequently under the guise of a relapse of influenza, pneumonia or other inflammatory complications first appear.

The real influenza relapses are due to the germs remaining from the first attack, which suddenly multiply again and subject the incompletely immunized patient to a fresh attack of influenza. Certain bacteriologic investigations make it likely that the germs in convalescence may remain in an attenuated form perhaps for fourteen days or longer in the various cavities of the human subject, and later on again become virulent. But in these late relapses, especially during an epidemic, a new infection is just as probable. Overzealous contagionists, to save their theory of immunity, have denied these reinfections and have sought to explain these attacks as late relapses or simple coryza. (Compare p. 578.) It is not clear to me how this helps the doctrine of immunity. As far as theory is concerned, it is surely immaterial whether the influenza arises anew, after two to three weeks, from the residual germs (relapse) or from freshly introduced germs (reinfection). In both cases the patient demonstrates that he has not been absolutely immunized by the first attack. [The disease is sometimes continued in the form of *chronic influenza,* in which the bacilli do not disappear and lead to chronic bronchitis or chronic pneumonia. (See p. 632.) Such cases may have any of or all the symptoms of an acute attack at various and irregular periods, while enjoying comparatively good health in the intervals.—Ed.]

DIAGNOSIS.

Wherever the specific bacilli are found, the diagnosis is certain. But even apart from this, the manifestations of influenza in the pronounced and typical varieties are so characteristic that the disease can generally be easily and certainly recognized. This is especially the case during the prevalence of large epidemics. Unquestionably during such times numerous diseases resembling influenza, which, if there were no epidemic, would certainly be given a different name, are called influenza, but the mistake is statistically insignificant in comparison with the enormous number of correct diagnoses, and is more than compensated by the fact that numerous complications of influenza, namely, pneumonia, pleurisy, etc., are not recognized as the results of influenza, but are registered as ordinary pneumonia, pleurisy, etc. A glance at the general mortality lists of penumonia, acute diseases of the respiratory organs, and tuberculosis in the pandemic periods will at once prove this point. (Compare p. 568.)

After the great epidemics, physicians, and more particularly the laity, are very prompt with their diagnosis of "influenza," so that the well-known saying, "What one cannot bend," finds general application. Gradually the remembrance of the former great epidemics disappears, until finally the new generation of physicians has a practical interest only in the disease *influenza nostras*, or "la grippe," and for *influenza vera* merely a historic interest.

The differential diagnosis between a mild rudimentary influenza and intense coryza is possible only by means of a bacteriologic investigation. The same is true of the differential diagnosis between *influenza nostras* and *influenza vera*, especially in non-epidemic periods. Clinically it is often as impossible to separate them as it is to distinguish *cholera nostras* from *cholera Asiatica*.

Yet there often are decisive clinical distinctions between *influenza vera*, on the one hand, and catarrhal fever, or "grip," on the other. A sudden onset with rigors and high initial fever, the severe prostration, the intensity of the nervous symptoms, the occasionally exclusive nervous character of the disease, without any respiratory symptoms, all point to *influenza vera*. If to these pneumonia is added in strong young individuals, the probability of the epidemic being *influenza vera* is much increased, because although endemic grip occasionally gives rise to a capillary bronchitis or catarrhal pneumonia, this occurs only in old, decrepit individuals and in small, weakly children. Finally, if the other severe complications are observed, especially in the respiratory system (abscess and gangrene of the lung or acute double pleurisy), in the cerebrospinal system (coma, meningitis, encephalitis, multiple neuritis, etc.), and in the digestive tract (hemorrhagic enteritis, etc.), every physician will recognize, even without a bacteriologic investigation, that he has to deal with an epidemic of *influenza vera*, even if the epidemic is local—that is to say, occurs during a non-pandemic period. The bacteriologic demonstration of the specific influenza bacilli, provided that in the future, too, they remain the only proved cause of *influenza vera*, will add absolute certainty to the clinical diagnosis of such epidemics.

[DIFFERENTIAL DIAGNOSIS.

During an epidemic, or in its typical form, influenza presents no difficulty of diagnosis; at other times or in other forms a positive immediate diagnosis may be well-nigh impossible. The chief diseases from which influenza has to be differentiated are measles, scarlet fever, and enteric fever, also simple coryza, bronchitis, and miliary tuberculosis. Moreover, influenza may occur concomitantly with any of these diseases, —especially, in infancy, in conjunction with scarlet fever or measles,— and under such circumstances even the discovery of the specific bacillus will not, as it generally does, clinch the diagnosis.

From Measles.—Since conjunctivitis, laryngitis, bronchitis, tonsillitis, frontal headache, etc., are common to it and influenza, a certain diagnosis may not be possible before the fourth day, when the fresh febrile accession and appearance of the rash indicate measles. According to Franke, a streaky erythema limited to the anterior pillars of the fauces is pathognomonic of influenza. Very often it is accompanied by enlargement of the anterior papillæ of the tongue. On the other hand, Koplik's spots and general erythema of the pharynx and gums would be diagnostic of measles. Süsswein states that influenza often complicates measles in young children and influences it unfavorably, but the mixed cases may be clinically indistinguishable from measles.

From *miliary tuberculosis* influenza can generally be distinguished by the coryza and conjunctivitis, and from *simple coryza* or *bronchitis* by the sudden onset, rapid course, nervous symptoms, rash, and enlargement of the spleen.

From Enteric Fever.—For the first few days a definite diagnosis may be impossible. If the attack of influenza commences with gradual pyrexia, with diarrhea, rose-spots, and enlargement of the spleen, as happens occasionally, we may have to wait until the temperature begins to fall before the diagnosis becomes certain. Additional doubt will arise if epistaxis and nervous symptoms, signs common to both diseases, are also present. The most useful guides are then the coryza and conjunctivitis, more characteristic of influenza, while a relatively slow pulse and a positive serum-reaction would be in favor of enteric fever. Leukocytosis is absent in both diseases when uncomplicated.—ED.]

THE FEVER OF INFLUENZA.

Under fever symptoms we shall refer only to the variations of body temperature. With the initial chill the body temperature rapidly rises. Only in a few cases has the temperature been taken at the time of the chill, and it has then been found, as in several of our hospital cases (especially doctors and nurses), to be 40° C. or higher. This initial rise of temperature is, in mild cases, often the highest during the whole course of the disease. A rapid rise of temperature is the rule, but in some cases the temperature rises gradually, the acme being reached on the second or third day. The duration of the fever is generally that of the attack; in simple influenza, from one to several days. Frequently, however, the fever disappears before the other symptoms of influenza, and, indeed, not uncommonly there is a great disproportion between the height of the fever and the intensity of the other symptoms—a further proof that the nervous symptoms and the general phenomena of influenza are not dependent upon the rise of temperature.

Should the fever be protracted, the curve may have one of several forms. Like Kormann, we have noted a type of high continued fever (39° to 40° C.) lasting several days, and terminating either rapidly or gradually. More frequently it is of a remittent or intermittent type, with the ordinary morning remissions, or of the *typus inversus*, or quite irregular.

The temperature, even in simple cases, usually reaches 39° C. at some time during the course of the disease; generally it rises even higher. Temperatures of 40.5° or even of 41° C. (O. Frentzel), even in uncomplicated cases, lasting but one, two, or three days, have been observed, although a moderate degree of fever is the general rule in simple cases.

It is possible that an afebrile course, as noted by many authors, may occur in very rudimentary and abortive cases. Eichhorst states that "afebrile cases of influenza are not at all uncommon, and they are especially characterized by severe nervous symptoms." Without doubt in such seemingly afebrile cases the transitory initial rise has remained unrecorded because the temperature was not taken at the time. It is certainly not proper without further data to class as afebrile those cases which began with decided chilliness or rigors, even though during the time that they were under observation by the physician they had no fever.

So-called *hyperpyrexial* temperatures (41.5° to 41° and over) are not at all uncommon for a short time in simple influenza,* but they are more frequent with certain complications.

These marked hyperpyrexial temperatures have been noted especially in the rare cases where influenza sets in with severe cerebral symptoms, loss of consciousness, coma, hemiplegia (encephalitis grippalis), and soon terminates fatally.

Defervescence may be either rapid, especially in cases lasting only one or two days, or gradual, with steadily diminishing diurnal excursions.

A phenomenon, to whose frequency I can testify, considered by Teissier and others to be almost pathognomonic, is a fall of temperature for one or two days, while the other influenza symptoms continue, this being followed by a recurrence of the fever lasting from one to several days, generally with an increase of all the other symptoms of the disease. Krehl says: "Frequently several days of normal temperature are interposed between these febrile periods." This may be called a bileptic or polyleptic influenza. Thus we have a marked tendency to relapse indicated already in the course of the attack of influenza, caused, no doubt, by a cumulative production of pyogenic or other toxins, which are then absorbed and enter the circulation.

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* "Child, nine months old; sudden onset of the influenza with severe convulsions. Two hours later temperature in the rectum 41.3° C. Mild course." (My influenza lectures, p. 25.) The German army report mentions a case of influenza pneumonia with a temperature of 41.5° C. *intra vitam* and of 43° C. (?) five minutes after death.

We must mention here an important but rare form of the fever, which has been frequently emphasized in literature and is well known to us.* We refer to the cases of protracted pyrexia in uncomplicated influenza in which the fever shows a regular quotidian intermittent type. Since in such cases, during the intermission, the other influenza symptoms are also less prominent (euphoria), and the rise in temperature is always sudden and often accompanied by a rigor, while the defervescence is accompanied by sweating, the picture of such an influenza attack closely resembles an *intermittent quotidian* fever. It is probably such cases which have given rise, in times past and present, to the erroneous view that influenza was a modified malaria. We would explain these cases as resulting from a periodic activity of the influenza bacilli in the formation of their pyogenic products.

Lastly, there are those rare, diagnostically deceptive cases in which the disease, after a typical onset, lasts for two or three weeks, with high continued fever (39° to 40° C.), but without any respiratory or other complications, and occasionally with but slight development of nervous symptoms. The temperature-chart resembles that of enteric fever, but all the other signs, namely, the sudden onset with rigor, the general appearance of the patient, the absence of cerebral symptoms, of the dry tongue, of meteorism, of roseola, and of diarrhea, exclude even the possibility of an abnormal attack of enteric fever. In these cases influenza appears as a protracted febrile affection without any localizing symptoms (Hagenbach).

This is the protracted form of the pure influenza fever, due, apparently, to a continuous formation of pyogenic products by the specific bacteria. That there is no definite proportion between the production of the pyogenic and the neurotoxic poisons appears obvious from the disproportion between the febrile and the nervous symptoms.

In the following description of the symptomatology of influenza we shall consider the separate organs in detail. It will not be possible to mention all the immense literature in this field, and we shall have to limit ourselves, even as regards those writers who have assisted in building up the clinical pathology of influenza.

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* Influenza lectures, p. 25, Kornblum, *loc. cit.*

SYMPTOMS RELATING TO THE RESPIRATORY APPARATUS.

Even although numerous influenza cases run their course without any symptoms referable to the respiratory apparatus, as, for instance, in the purely toxic forms (compare p. 591), nevertheless the rule holds good that by far the most numerous and important of the local inflammations due to influenza occur in the different parts of the respiratory mucous membrane, from the nose to the alveoli of the lung.

These phenomena depend upon the fact that the specific cause of influenza settles first on the respiratory mucous membrane, which becomes the seat of the primary lesion.

To this statement we should add another explanatory one, which I made use of in my lectures on influenza in the spring of 1890: "The catarrh of influenza does not always, nor even as a rule, progress from the nasal cavities downward to the entire respiratory tract. Any section of the membrane alone may be affected without any implication of the remainder. A nasopharyngeal catarrh alone is common; but there are also cases in which the larynx alone is affected. The cases in which the trachea and the large bronchi were the principal parts affected frequently showed convulsive attacks similar to whooping-cough. The bronchi, bronchioles, and alveoli, however, may be the only portions affected. There is also a very acute primary influenza pneumonia, that is to say, an influenza which commences with all the symptoms of pneumonia." We shall recur to this later, and shall here consider the separate portions of the respiratory apparatus.

The Nasopharynx and the Adjacent Cavities.—In many cases there is a pronounced rhinitis; many patients complain of a cold in the head, with the accompanying loss of smell. The general appearance of the patient, the reddened nostrils, the reddening and swelling of the eyelids, the conjunctivitis, the copious flow of tears, the "watery eyes," so frequently mentioned, the flushing of the face, especially in the supra-orbital region, present the typical picture of an intense coryza. Yet those authors too are right who, apart from fever and the other severe symptoms of the disease, differentiate the coryza of influenza from the common coryza, which is described as "a coryza with a plentiful watery secretion and frequent sneezing," but is quite rare in true influenza. Based on this definition, the statement of Maillart, Hertz, and others, that coryza "is an exceedingly rare complication of influenza," is comprehensible.

Some authors collected statistics of the frequency of coryza in influenza. In the Leipsic City Hospital Krehl found it in 79 per cent. of the cases; Robertson and Elkins (Edinburgh), in 77 per cent. In the Hamburg Hospital, according to Schulz, it occurred in 50 per cent.; in the Julius Hospital at Würzburg, according to Anton, in 25 per cent. of the cases. Biermer and Litten, the latter upon the basis of the German collective reports, note: "Almost without exception the symptoms of coryza are present"; Teissier: "Coryza is the rule." A flowing coryza Preston found in only 8 per cent. of the cases; but Bristowe saw "watery eyes" in 96 per cent. of the cases.

We can only once more emphasize the fact that both the subjective and the objective signs of coryza are absent in quite a number of cases. Rhinoscopy may show "an abnormal, intense reddening of the nasal mucous membrane," but it is quite overshadowed by the severity of the other symptoms and remains unnoticed by the patient. Ruhemann says: "As regards rhinitis, it cannot be said that either in intensity or in extent has it been so marked as in many of the former epidemics."*

The acrid nasal discharges excoriating the upper lip and the attacks of sneezing were much fewer in the epidemic of 1889–1890 than in former influenza epidemics. Epidemics evidently vary in this respect.

Very often the catarrhal inflammation extends from the nose to the frontal sinus, to the ethmoid sinus, and to the antrum of Highmore. Weichselbaum regularly found in his autopsies catarrhal or purulent inflammation of the nasal sinuses. It is probable that the terrible frontal headaches, which may last far into convalescence, are due to a local inflammatory process in the frontal sinus. In quite a number of cases purulent inflammation of the ethmoid sinus, and especially empyema of the antrum of Highmore, occasionally also of the temporal cavities, occurred, as operations upon these cavities subsequently demonstrated.

These chronic influenza empyemata of the nasal cavities occasionally gave rise to stubborn "neuralgias" in the supra-orbital and infra-orbital regions, until their cause was ascertained and relief afforded by operation. In the pus of such an empyema we once found typical influenza bacilli.

Epistaxis, in our experience, is very rare. Litten, on the other hand, says (German collective reports): "Epistaxis during this epidemic (1889–1890) was frequently noted and was occasionally so profuse that the observers often declared it to be almost uncontrollable." Most statistics entirely ignore epistaxis. Anton and we ourselves estimate it to occur in 2 per cent. of cases; Bristowe does the same. In descriptions of some former epidemics (1582, 1732, 1758, and 1803) the frequency of epistaxis is especially mentioned.

The Larynx.—There can be no doubt that the larynx is much oftener affected than the subjective sensations of the patient or the objective signs, unaided by laryngoscopic examination, would lead us to suspect. That a laryngoscopic examination was made in so small a number of cases is easily understood from the fact that during the influenza pandemic the demands on the doctors' time left no leisure for such examinations.

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* "Le nez destillait sans cesse comme une fontaine," Pasquier, Epid. 1557.

An intense laryngitis, with hoarseness, occasionally even with laryngeal dyspnea, was noted by us in 6 per cent.; by Krehl (Leipsic), in 5; by Stintzing (Munich), in 7; and by Schulz (Hamburg), in 16 per cent. of the cases.

Intense hyperemia and edema were the principal symptoms. No doubt these conditions occasionally developed secondarily to the terrible paroxysms of coughing. Acute inflammatory edema of the glottis, necessitating tracheotomy, we noted in a girl aged nineteen upon the third day of her attack of influenza. "In this case there was neither coryza nor the signs of tracheitis or bronchitis. The larynx alone was the seat of a severe inflammation. The abscess of the larynx opened spontaneously some days after the tracheotomy had been performed, with a copious evacuation of pus."* Cases of acute edema of the glottis were described by Petrina, Landgraf, and Norris-Wolfenden; Duflocq considers it to be a frequent occurrence. Cases of inflammation of the larynx with resulting abscess formation, viz., of phlegmonous laryngitis, were described by H. Rieger, Rethi, M. Schaffer, and by the latter as a sequela of influenza. A case of laryngitis ulcerosa hypoglottica, with gangrenous ulcers, is mentioned in the German army report, and Rethi describes a case of perichondritis thyreoidea.

Hemorrhagic laryngitis, the laryngoscopic picture of which we cannot describe here, was observed by us in three cases. The relative frequency of this hemorrhagic variety is noted in the descriptions of Löwenstein, B. Fränkel, Heymann, Marano, and others.

It is important to remember that an admixture of blood with influenza sputum may be due to hyperemia of the laryngeal mucous membrane. Thus Leyden reports cases of hemorrhage from the larynx. Subglottal edema, laryngitis hypoglottica, isolated edema of the interarytenoid folds, slight ulcerations of the vocal cords (Le Noir, Betz, Klebs, Kuskow), and laryngitis crouposa have also been observed.

Paralysis of the muscles of the larynx or of the recurrent laryngeal nerve after influenza have now and then been seen, either isolated or in combination with other paralyses. Two cases of paralysis of the posticus are noted by Rethi.

Trachea and Bronchi.—Hyperemic and inflammatory processes in the bronchial mucous membrane are among the most frequent and important local affections of influenza. To our previous statement above, that any part of the respiratory apparatus may be affected primarily and alone, we may add that subsequent extension of the inflammatory process to other parts of the respiratory apparatus is the rule.

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* Our influenza lectures, p. 27.

The implication of the trachea can be directly observed on laryngoscopic examination by the intense scarlet appearance of its mucous membrane. It is further characterized by the tickling and burning pains along the course of the trachea and under the sternum. Pressure upon the sternum is painful and often produces cough.

The convulsive paroxysmal cough which so often occurs as a symptom of the influenza bronchitis depends, in our opinion, upon the inflammation of the trachea, especially at the point of bifurcation, and of the main bronchi. Many deem this cough to be a nervous phenomenon and say that it is due to a direct irritation of the cerebrospinal cough center by the toxins of influenza. As against our view, they affirm that this spasmodic cough frequently has no relation to the perceptible auscultatory bronchial phenomena and that it is often absent in widely disseminated, intense bronchitis. It is obvious that these objections to our opinion of the tracheobronchial origin of the spasmodic cough are irrelevant.

The spasmodic cough often occurs in paroxysms, especially at night, or at definite times during the day; sometimes it torments the patient continuously. Severe attacks of suffocation even may result.

The observers of some of the oldest epidemics already emphasized the severe, spasm-like character of the cough of influenza. Th. Short, in 1510, mentions it as a "terrible tearing cough, . . . so violent a cough that many were in danger of suffocation." The fact that the name "Coqueluche" was applied first (1510) to influenza and later transferred to whooping-cough, probably depends on the characteristic spasmodic cough which occurs in both affections. On account of the loud cough the influenza of 1580 was called "sheep's cough." Pasquier attributes to the violent cough in the epidemic of 1410 the frequent hemorrhages and the abortions in pregnant women.

Catarrh of the air-passages was noted in Hamburg (Schulz) in 53 per cent.; in Leipsic (Krehl), in 82 per cent.; in Würzburg (Anton), in 59 per cent.; in Munich (Stintzing), in 57 per cent.; and by Robertson in 77 per cent. of cases.

The *bronchitis of influenza* is sometimes diffuse, distributed over most of the bronchial ramifications, sometimes limited to one lobe of the lung, and quite sharply defined. The latter is an important peculiarity of the bronchitis of influenza, and points to the localized development of the specific bacilli in definite parts of the bronchial tract.

When bronchitis affects one or both upper lobes only, a doubt often arises whether we have not to deal with an apical pulmonary phthisis.

The dry or moist character of the bronchitis is further characterized by either the absence of any sputum or by copious expectoration which may increase to a veritable bronchorrhea. The auscultatory phenomena are very manifold, depending, as they do, on the extension of the bronchitis into the larger and medium-sized bronchi or even into bronchioles. The thorax of influenza patients often presents a truly diagrammatic picture of the most diverse kinds of rhonchi.

Of special interest are those cases to which Graves and Biermer have called attention, in which a marked dyspnea exists unaccompanied by any abnormal physical signs. The respiratory murmur is everywhere vesicular. There may be a râle here and there, but nothing to point to a central pneumonia; sputum is entirely absent. Graves thought these cases were the result of a direct irritation of the vagus, and emphasized the remittent or intermittent character of the dyspnea. We agree with Biermer's interpretation; he says: "It seems to us more likely that a congestion of the lung, which occurs so frequently in influenza, and so long as there is no edema gives but few signs on percussion or auscultation, is the cause of this exaggerated dyspnea."

The sputum in influenza bronchitis varies. "Characteristic influenza sputum" is frequently mentioned. But there are various kinds. Especially characteristic is the copious sputum which is often expectorated in remarkable quantities, which we frequently found collected in several vessels on making our hospital round. In these cases a large layer of white or dirty-gray foam lies on top; next follows a layer composed of a quantity of turbid serous material in which purulent flakes are suspended, forming the principal portion, while the bottom of the receptacle is covered by a thin layer of vitreous-like mucus or by a turbid deposit. Another highly characteristic variety of sputum is found early at the height of the influenza attack; it is an almost purulent, nummular, occasionally globular sputum, in the latter case quite like the cavernous expectoration of tubercular individuals. The "yellowish-green nummular sputum" is considered by R. Pfeiffer as "a characteristic peculiarity of influenza." There is yet a third variety of sputum to be mentioned as frequently occurring in influenza bronchitis, in which bloody streaks or pure blood of dark-red color, either nummular or globular in shape, is mixed with the purulent or serous expectoration, reminding one of the sputum in infarction of the lung. This is due to a rupture of vessels in the hyperemic bronchial mucous membrane, either spontaneous or caused by the exertion of coughing (bronchitis hæmorrhagica grippalis). The bronchitic hemoptysis in influenza was mentioned already by Nelson (1803), Leared (1862), and others.

If the influenza bronchitis extends diffusely into the bronchioles, there arise dyspnea and cyanosis. Old decrepit individuals, tuberculous patients, and weak, rachitic children may succumb to this diffuse capillary bronchitis at the height of an influenza attack without any associated pneumonia.

An almost unnoticed fact is the occurrence of an acute bronchiectasis of the middle and smaller bronchi during the influenza attack. We have seen many instances of this condition at postmortem examinations. This possibility must also be kept in mind during life, if, after an influenza has run its course, there should persist, over one or more pulmonary lobules with a normal percussion-note, numerous large vesicular metallic râles and copious sputum of a bronchiectatic character. Such cases of bronchial dilatation may last weeks and even months and yet terminate in complete recovery. This was the case in one of our patients in whom, on account of their long duration, we had thought that the bronchiectatic cavities and interstitial changes would be permanent. In consequence of the bronchial dilatation a fetid, putrid bronchitis may also arise.

The occurrence of a fibrinous or croupous bronchitis with or without pneumonia has been noted in the recent epidemics by Naunyn and Weichselbaum, and by Nonat, Magendie, Caseaux, Legendre, in the earlier epidemics.

It will be appropriate to describe here the anatomic picture of influenza bronchitis. It is characterized by an exceptionally intense hyperemia of the mucous membranes, extending into the finest bronchi. On pressure the lung exudes, on to the dark-red, cut surface, numerous large and small tenacious, whitish-yellow drops of pus from the severed bronchi. Kundrat correctly states: "These bronchitides were characterized both by their extent and by their intensity, inasmuch as not only the bronchi of the posterior but also those of the anterior and superior portions of the lung were found occluded. Not only the finer, but also the middle-sized, bronchi were occluded by thick, mucopurulent secretion, clumpy in the larger bronchi, and giving the impression that the individuals had been suffocated by their bronchial secretions." This is the "catarrhe asphyxique grippal" of Netter.

We shall give only a brief description of the *finer histologic changes* which influenza produces in the respiratory mucous membrane. They have been described by the pathologists: Ribbert, Klebs, Kuskow, Marchand, and others.

The chief point is the enormous hyperemia, which not rarely gives rise to extravasation of blood. Attention is also called to the profuse cellular infiltration, which, according to Kuskow, often gives rise to the formation of "small lymphomata." Furthermore, the frequency and significance of thrombosis are commented upon, especially by Klebs and Kuskow. Klebs mentions only "capillary thromboses," while Kuskow considers thromboses of the smaller arteries and veins more common. The thrombi consist of small, finely granular, fibrinous masses, which gradually assume a more homogeneous character until they appear hyaline. Micro-organisms occasionally, although rarely, give rise to the formation of numerous obstructing thrombi. Kuskow also describes hypertrophy and exfoliation of the vascular endothelium and the resulting "desquamation thrombi."

Obstruction of the larger capillary areas causes necrosis of the mucous membrane, which is generally confined to the superficial layers; nevertheless, on one occasion Kuskow found a necrosis extending deep into the submucosa, with exposure of the cartilages of the trachea and of the larger bronchi, together with an ulcerative tracheitis and bronchitis analogous to the ulcerative laryngitis previously mentioned.

The processes affecting the tracheobronchial mucous membrane, already described,—hyperemia, small-celled infiltration, thrombus formation,—occur in a similar manner and even in a more marked degree in the lungs. The disposition of inflammatory pulmonary processes occurring during influenza to abscess and gangrene formation is thereby easily explained.

The conception arrived at by Klebs, which was based upon an anatomic investigation, is worthy of mention. In his opinion the processes taking place in the blood constitute the primary and most important phenomena in influenza. The apparently primary catarrhal and inflammatory manifestations, which, according to the opinion of many, represent the essential points of the process, are, according to Klebs, nothing else than the results of the obstruction of large capillary areas by thrombi. These are formed by granular masses in the blood derived from the leukocytes and erythrocytes. From the resolution of these soft granular masses are formed masses of thrombi becoming more and more homogeneous. The obstruction of larger capillary areas causes hyperemia of the neighboring capillaries, inflammation, and exudation, and favors the deposition of pathogenic micro-organisms, which find a suitable soil in the tissues injured by the thrombosis.

Klebs would also attribute the cerebral manifestations and other functional affections of the nervous system, as psychoses, somnolence, and coma, to circulatory disturbances, which in their turn have arisen from capillary thromboses. He believes that, as compared with these anatomic phenomena, the toxic influences play but a small part. Our clinical experience does not agree with the hypotheses of Klebs.

INFLUENZA PNEUMONIAS.

ANATOMIC AND BACTERIOLOGIC VARIETIES.

Pneumonia is the most frequent and most important complication of influenza. It is the decisive factor in influencing the mortality of the disease.

The question regarding the relation of influenza to pneumonia has at all times, and more particularly at the beginning of the pandemic of 1889, been answered in a variety of ways. When the generally received opinion that influenza was a harmless disease made way for the recognition that it could give rise to grave and fatal inflammations of the lung, there were, nevertheless, some authorities who attempted to explain the coëxistence of influenza and pneumonia as purely accidental, and due to the simultaneous existence of an influenza epidemic and an independent pneumonia epidemic.

A glance at the history of influenza teaches that there has never been any epidemic which has not been marked by frequent pneumonic complications. Already in the epidemic of 1580 this had been emphasized by Bockel, and even more by Sydenham (1675), Arbuthnot (1732), Huxham (1737), Whytt (1758), and others. But the epidemics of 1830 to 1837 especially gave rise in France to a lively discussion regarding the character of the influenza pneumonia. The question whether pneumonia was only a complication, "une maladie surajoutée" (Vigla, Petrequin, Nonat), or the localization of the pathologic process in the lung, "une symptome essentiel de la grippe" (Landau, Piorry, Gouraud), was discussed at that time just as vigorously as it is at the present time. The reports of the French physicians at that time form a veritable mine of accurate observations concerning the peculiarities of influenza pneumonia, and the ways in which it differs from pneumonia. The pneumonia of influenza had been designated already by Sydenham as "sub alio sidere nata."

Another view was that the influenza bronchitis merely brought about the disposition and prepared the soil upon which the ubiquitous pneumonia germs could settle and develop (secondary infection). Certain instances that could not be ignored, in which unmistakable influenza and pneumonia set in together, were explained by the supposition of a simultaneous double infection with the bacilli of both influenza and pneumonia. This view gained many supporters when bacteriologic examinations showed the presence of the well-known micro-organisms of pneumonia in influenza-produced inflammations of the lung.

Remarkable differences of observation occurred here. The majority (Weichselbaum, Bouchard, Netter, Ménétrier, Birch-Hirschfeld, and many others) found the Diplococcus lanceolatus almost exclusively, while others (Finkler and Ribbert, Vaillard and Vincent, and others) found only the Streptococcus pyogenes. To explain these facts it was assumed that the first group of observers met only with croupous influenza pneumonia, in which the diplococcus is supposed to be the free dominant organism, while the other group came across only catarrhal or bronchopneumonias, in which the streptococcus is supreme. Numerous other observers found both diplococci and streptococci besides; occasionally, staphylococci and Friedländer's bacillus. In order not to disturb anatomic and bacteriologic classification, we must suppose that these were cases of mixed pneumonia, croupous-catarrhal, or, as we shall call it for the future, cellular-fibrinous mixed pneumonia.

The doctrine that pneumonia was due exclusively to either mixed or secondary infection seemed thus so firmly established that it required some courage to go against the stream and to assume that the still unknown exciting cause of influenza was in itself capable of causing an inflammation of the lungs. Was there any reason why this microbe, which was evidently able to cause the most intense inflammation of the bronchial mucous membrane, even extending into the finest bronchioles, should not also penetrate into the alveoli? Were the alveoli actually accessible only to the diplococci and the streptococci that cause pneumonia? Reflections such as these, but especially a series of clinical and anatomic experiences, led me, in December 1889, to put forward the theory which, in earlier epidemics, already had been precisely stated by the physicians at that time (Gray, 1782), namely: "There is a primary influenza pneumonia (that is, an inflammation of the lung caused by the influenza toxin) whose onset is often simultaneous with the typical manifestations of influenza." I called this "the pneumonic form of influenza."

Similar views were put forward at that time (1890) by Drasche, Runeberg, and Heitler. Drasche says: "Although in the majority of cases influenza pneumonia is preceded by bronchitis, from which the inflammation extends into the lung tissue, nevertheless clinical observation shows that the lung-affection may occur as a direct result of the infection without any sign of bronchitis." Heitler states: "From our knowledge at the present time regarding the character of pneumonia there is no reason from a clinical, anatomic, or bacteriologic standpoint, for not considering many cases of croupous pneumonia during the influenza epidemic as a direct result of the causative agent of influenza."

Our view was not accepted at that time by the bacteriologists, who insisted upon mixed infection with the known micro-organism of pneumonia, and it was condemned as "untenable."

Two years later, when the influenza bacillus was discovered, the question of the etiology and pathogenesis of influenza pneumonia assumed a different aspect. First R. Pfeiffer and then Beck and Wassermann showed that in the pneumonic exudate within the alveolar lumina, as well as in the alveolar septa (and here particularly inclosed in round-cells), influenza bacilli were to be found in "remarkable numbers." Pfeiffer describes his discovery in the words: "In smear preparations that have been prepared from the secretion adhering to the mucous membrane of the larynx and trachea there is generally a mixture of various varieties of bacteria, streptococci, diplococci, etc., but even here the influenza bacillus is by far the most numerous. In the larger bronchi the admixture of other bacteria becomes less; in the bronchioles filled with purulent material the influenza bacillus is predominant; so, too, in the pulmonary tissues. The other micro-organisms, streptococci and diplococci, are not seen, in recent (pneumonic) attacks, either in sections or in smear preparations.

Wassermann obtained similar results: "The opinion that influenza pneumonia is caused only by a mixed infection with pneumococci and streptococci would be tenable only if we were always to find pneumococci and streptococci in influenza pneumonia. But this is not the case; on the contrary, these micro-organisms are almost always absent, so that in pure and uncomplicated cases a pure culture of influenza bacilli is found in the pneumonic sputum. Therefore this form of pneumonia—and it is by far the most frequent in an epidemic—is not to be considered as a foreign complication of influenza, but simply as a continuation of one and the same process from the bronchi into the pulmonary tissues. In other words, influenza pneumonia is quite independent of ordinary croupous pneumonia, and is a separate variety.

Thus at last was influenza pneumonia, in the strict sense of the term, rightly classified from a bacteriologic point of view.

Anatomically this true pneumonia caused by the influenza bacillus is, according to Pfeiffer, Beck, and Wassermann, entirely catarrhal.

We cannot here consider further the exhaustive description which Pfeiffer has given of the pneumonia caused by influenza bacilli. It is but a repetition of what we have known long regarding the anatomic course of a pure catarrhal pneumonia.

As the inflammatory process proceeds from the bronchi into the pulmonary tissues, there arise, as always under such conditions, lobular areas of inflammation, which either remain separated by tissues containing air, or coalesce to secondary lobar areas whose origin from lobular foci can still be recognized. The cut surface is quite smooth, and on pressure drops of yellow pus ooze from the severed bronchi. Microscopically, "the whole appearance is one of catarrhal suppuration *in optima forma*. The alveolar lumina and septa, as well as the peribronchial connective tissue, are so infiltrated with round-cells that apparently the lung structure is entirely obliterated. In the alveoli surrounding these purulent infiltrations, besides containing round-cells, the alveolar epithelium is much swollen. In preparations stained by Weigert's method the absence of fibrin (or its occurrence at most in traces) in the areas of infiltration is very evident."

No doubt most of the bronchopneumonia caused by influenza accords with the bacteriologic-anatomic description of Pfeiffer. Nevertheless, there is also no doubt that much influenza bronchopneumonia is accompanied by streptococci, possibly also with diplococci, which settle along with the influenza bacilli and may even overgrow them. Only thus can we explain the numerous cases of influenza pneumonia in which streptococci and diplococci were found during the time of the pandemic of 1889–1890. Albu emphasizes the frequency of the secondary bronchopneumonias arising from the invasion of streptococci, and considers "this mixed infection as pathognomonic of influenza."

The pneumonia just described and caused by the influenza bacilli is a purely catarrhal form, and is by no means the only one which occurs in influenza. A very large number of cases are of the croupous variety, and a third not less extensive group consists of certain mixed pneumonias—that is, catarrhal-croupous or, as they may be called, cellular-fibrinous. We shall return to these varieties later.

Up to the present it has not been shown that the influenza bacillus, besides giving rise to a catarrhal inflammation, can produce also a fibrinous exudate in the pulmonary alveoli. The bacillus has not yet been found in croupous infiltrations. We must for the present assume that the croupous pneumonia which occurs so frequently in influenza is due to a mixed or secondary infection with those cocci which alone can produce the croupous inflammatory condition (Diplococcus lanceolatus s. pneumoniæ). We agree with the general prevailing opinion that this diplococcus is the main cause of croupous pneumonia, but we cannot overlook the fact that this question is as yet by no means settled.

A point upon which there has been much difference of opinion is the relative frequency of catarrhal and croupous inflammations of the lung in influenza. The reasons for contradictory opinions on this point are obvious. They depend upon the facts that at the bedside it is often impossible to differentiate between these two forms of inflammation; and that the anatomic differential diagnosis also is by no means always easy or certain.

It is in influenza especially that mixed and transitional forms of lobular and lobar infiltration, whose anatomic character, viz., whether catarrhal or croupous, is often extremely difficult, either macroscopically or microscopically, to recognize. In these mixed, that is to say, cellular-fibrinous, pneumonias, there are found, besides characteristically catarrhal pneumonic areas, also just as characteristic fibrinous fine- and coarse-grained foci in the same lobe of the lung; in some of the affected areas are found alveoli which contain catarrhal and fibrinous masses intermixed, so that the naked-eye appearance is not characteristic of either variety of pneumonia. But even microscopically the differentiation is often difficult. In the sections stained by Weigert's method several alveoli or groups of the same may show catarrhal inflammation (a cellular exudate with little or no fibrin), while other alveoli situated near by are infiltrated with round-cells, or these are even irregularly distributed among the alveoli, which may be filled with fibrin and thus exhibit the characteristics of true fibrinous pneumonia.

We cannot here dwell longer on the unsettled question of the pathologic anatomy of pneumonia, but we will quote some authors who refer to these mixed forms:

> Ziegler states that "the exudate of catarrhal bronchopneumonia may frequently have a hemorrhagic character, and that croupous exudations with fibrinous plugs also occur. These are cases, therefore, in which the cut surface shows a more or less pronounced pneumonic granular surface."
>
> Sahli points out that "bronchopneumonia, apart from its macroscopic dissemination, is histologically often difficult to differentiate from croupous pneumonia, and especially from croupous pneumonia in which there is hemorrhagic exudation, with a more or less appreciable amount of fibrin. In the sputum of such cases Fränkel's pneumococcus is not infrequently found, often also all or any of the other forms of micro-organisms which give rise to inflammation."

Kundrat, speaking of the bronchopneumonic areas in influenza, says that they are characterized by the fact that in the majority of cases the exudate is comparatively rich in fibrin, as shown to the naked eye by the granularity and solidity of the exudate.

We would lay particular stress upon the fact that also Weichselbaum found this blending of purulent and fibrinous infiltrated areas in bronchopneumonia due to the influenza bacillus. The bronchopneumonic areas are "reddish-brown and distinctly finely granular; other parts have rather the appearance of uniform hepatization. In the neighborhood of the purulent bronchopneumonic areas the alveoli contain, besides leukocytes, principally fibrinous exudate, whereas in other alveoli there is a serous or hemorrhagic exudate."

Below we give some statistics as to the frequency of the fibrinous and of the cellular pneumonias in influenza; the pathologic data naturally have a far greater value than the clinical data.

Birch-Hirschfeld found at the autopsies of 108 persons dying of influenza—

11 cases of croupous lobar pneumonia.
8 " " " lobular "
24 " " catarrhal "

He arrives at the remarkable conclusion that "in influenza the characteristic form appears to be croupous bronchopneumonia."

We found, in the autopsies on 32 cases of influenza pneumonias, 19 croupous and 13 catarrhal, including the mixed forms.

Naunyn reports that "in Strassburg typical lobar pneumonia occurred frequently as a complication of la grippe. Three such cases ran their course with the symptoms of an asthenic pneumonia; others terminated by crisis and were typical cases of croupous pneumonia. These pneumonias developed variously, at different periods in the course of the disease—often early and very acutely, at other times insidiously, from a bronchial catarrh; nevertheless at the autopsy they were typical fibrinous infiltrations."

Eichhorst especially emphasizes, in reference to the pneumonic areas, that "only in parts was the inflammation catarrhal; elsewhere the lung showed a decided fibrinous inflammation, in spite of the lobular dissemination of the disease."

Rollinger (Munich) found, among 10 influenza pneumonias, 5 croupous-lobar, 1 mixed lobar, 3 catarrhal, and 1 hypostatic pneumonia.

Marchand found, among 5 influenza pneumonias which he examined, 1 lobular pneumonia in which streptococci were found in pure culture; 1 multiple lobular pneumonia which consisted of firm, confluent areas of a brownish-red color and of a rather smooth cut surface; further, 3 lobar pneumonias in the state of reddish-gray or gray hepatization, "which were characterized by conspicuous softness, indicative of little fibrin and of many leukocytes." Marchand "cannot agree with the opinion that influenza pneumonia is of one particular variety only, and still less that it always depends upon a streptococcus infection, which is often probably accidental."

Ménétrier reports that the influenza pneumonias which terminated fatally "were nearly all croupous."

Hertz (Copenhagen) and Crookshank (England) emphasized the frequency of the croupous variety of pneumonia in influenza.

Weichselbaum found 7 croupous to 2 bronchopneumonias. He explains his finding of the pneumococcus in the sputum of influenza patients in the years 1889–1890 by the fact that the microscopic examination showed that in the majority of cases the inflammation of the lung was of a croupous character.

Biermer says: "The pneumonia is mostly of a catarrhal nature; croupous pneumonia also occurs, but is much rarer." Litten (German collective reports) quotes: "The characteristic of the present epidemic (1889–1890) was the frequent occurrence of croupous pneumonia, which occurred probably as often as the catarrhal form." H. Rieder (medical clinic in Munich) found, among 36 influenza pneumonias, 14 croupous (with 3 fatal cases) and 22 catarrhal (without a death). Krannhals (Riga) saw 53 cases of typical fibrinous pneumonias, 22 doubtful ones, and 37 of bronchopneumonia. Sokolowski (Warsaw) observed 14 croupous and 10 catarrhal cases. Hagenbach (Basel) especially notes that all influenza pneumonias observed in the Children's Hospital were of the croupous variety. Immermann says: "The great majority of the complicating pneumonias noted in the hospital was croupous. Demme (Children's Hospital in Berne) reports that the pneumonia was especially characterized as a catarrhal pneumonia. Yet 4 of 11 pneumonic cases had rusty sputum. Among the influenza pneumonias in the Strassburg epidemic of 1874–1875 R. von den Velden says that, "according to the course of the fever and the sputum, they were always recognized as belonging to the croupous form." Netter (Paris) describes the true croupous lobar pneumonia and its anatomic varieties, and, in particular, the frequent lobular-fibrinous inflammatory areas. But: "Plus frequent que la pneumonie lobaire est la pneumonie lobulaire." Stintzing (Munich), on the other hand, characterizes the greater number of his cases of pneumonia as bronchopneumonia (15 : 2), and Finkler found, among 45 cases of pneumonia, only 2 typically croupous. Guttmann, Merkel and Gutmann (Nuremberg), Albu, Lennmalm, and others saw only, or nearly exclusively, catarrhal pneumonia.

In addition to the voluminous literature already mentioned on this subject, the following extract may be added: At the meeting of the medical society of Leipsic (January 14, 1890) Heubner expressed himself in the following terms regarding the frequency of croupous pneumonia during the time of influenza: "Obviously this coincidental occurrence is not accidental. Influenza increases the disposition to acquire pneumonia, and makes the latter more severe. The character of the influenza pneumonia is an asthenic one. The severity of the secondary pleurisy is worthy of note." (Compare what has been said previously regarding pleurisy.)

These contradictions in the reports as to the frequency of both forms of pneumonia during the course of influenza are easily explained. To decide at the bedside whether we are dealing with a catarrhal or a croupous pneumonia is possible with certainty only in typical cases in which the croupous pneumonia begins and runs its course with its characteristic symptoms. These cases, however, form the minority;

most of the croupous pneumonia of influenza is characterized by a completely atypical clinical-pathologic course, so that the differentiation from bronchopneumonia is practically impossible. Nevertheless, I am in accord with the majority of observers and authors just quoted, not only from clinical knowledge, but from knowledge derived from the postmortem table, that the frequency of catarrhal bronchopneumonia during influenza has been considerably overrated. Physicians who, observing the onset of pneumonia in numerous small localized areas; the stoppage or the slow spread of the infiltration; the purulent character of the sputum; the onset of the disease without a chill; the remittent temperature-curve; the absence of true crisis—concluded that these were cases of catarrhal bronchopneumonia, must certainly have arrived at this conclusion in many cases which were really croupous pneumonia. On the other hand, we readily admit that many cases of pneumonia complicating grip, especially the acute lobar form, may have been mistaken for croupous pneumonia, when in reality it belonged to the catarrhal variety. With the outbreak of influenza physicians were confronted with an entire novelty, for catarrhal bronchopneumonia, which up to that time had been known only as a secondary affection, arising in the course of measles, diphtheria, whooping-cough, rickets, or in the latter stages of an attack of enteric fever, arising almost exclusively in children or aged persons with weakened constitutions, now appeared suddenly in the influenza epoch in an acute form, in many cases as a primary affection occurring in strong young persons who had up to that time been quite well, in whom any acute attack of pneumonia, even if it should run an atypical course, would be rightly termed croupous pneumonia.

A definite diagnosis regarding the variety of the pneumonia arising in the course of influenza can, as has been previously mentioned, only occasionally be made at the bedside. There is, strictly speaking, but one clinical sign, which points absolutely to the croupous variety, namely, the typical rusty sputum. On the other hand, a purulent sputum does not by any means exclude croupous pneumonia. (See p. 618.) The lobular character of the inflammation and its gradual development to a compact infiltration occur in both the cellular as well as in many of the croupous forms. The acute lobar infiltration is certainly more characteristic of fibrinous pneumonia, but it occurs also in the acute lobular-cellular pneumonia.

We are, therefore, at the bedside thrown back on the bacteriologic examination of the sputum. The finding of influenza bacilli in the sputum establishes the disease as influenza. If they alone are found in the sputum and the case is one of pneumonia without rusty sputum, it is probably a true influenza pneumonia due to the bacillus of Pfeiffer. Finding only diplococci or streptococci in the sputum is evidence for the case being respectively croupous or catarrhal pneumonia. [A rapid disappearance of the bacilli from the sputum is often associated with aggravated toxic symptoms.—Ed.]

Even so, the diagnosis is not so simple. One must be careful in drawing conclusions from the bacteriologic appearance of the sputum to determine the character of the pneumonia of influenza. It is sufficient, for example, to call to mind the fact that while Pfeiffer found in the inflamed parenchyma of the lung only the influenza bacillus, in the trachea and the larger bronchi he found a mixture of different varieties of bacteria, streptococci, and diplococci, although even in this situation the influenza germs were regularly in the majority. Probably the opposite condition may also occur: Diplococci and streptococci in the inflammatory areas of the lung, influenza bacilli in almost pure culture in the bronchioles and bronchi, from which the chief amount of the sputum is derived. Thus Albu found in one patient, in the sputum, a pure culture of influenza bacilli, but in the serous pleural effusion, due to a preceding pneumonia, he found a pure culture of streptococci.

Before we discuss more in detail the clinical and pathologic characteristics of the croupous influenza pneumonias, it may be proper to call attention to a fact regarding the question as to the frequency of croupous pneumonia in influenza, which up to now has been almost totally neglected.

Wherever accurate statistics derived from a large amount of material have been tabulated at the time of the influenza pandemic, and wherever an attempt has been made to distinguish between pneumonia caused by influenza and the cases of primary genuine croupous pneumonia occurring during the same period, it has appeared that the frequency of croupous pneumonia increased considerably at the time of the occurrence of an epidemic of influenza.

In my lectures of 1890 I demonstrated this fact with details and convincing statistical curves. Since it was noted everywhere, in Berlin, Vienna, Paris, Cologne, Munich, Marburg, Würzburg, Riga, Moscow, Warsaw, and Boston, it cannot have been due to a coincident occurrence of influenza with an epidemic of croupous pneumonia, as some authors assumed at the time of the pandemic, but it proves, on the other hand, that numerous cases of pneumonia during the prevalence of influenza, which, on account of their clinical course and the postmortem examination, were believed to have been genuine croupous pneumonia, were of influenzal origin. From this we infer that influenza more frequently gives rise to true croupous pneumonia by mixed infection than is admitted by many.

Concerning this, Curschmann expressed himself as follows in the meeting at Leipsic above alluded to: "Also the fibrinous pneumonia not complicated with influenza presents an unusual picture during the epidemic." Curschmann too emphasizes the frequency and intensity of the pleurisy accompanying influenza pneumonia.

We would refer our readers to our previous section on Mortality. (See p. 568.) We give here the mortality from pneumonia in Vienna during the time of the pandemic of 1889–1890, according to weeks: The first week in December, 40 cases; second week, 56; third week, 51; fourth week, 124;* first week in January,* 170; second week,* 123; third week, 66; fourth week, 56 cases (according to Drasche). The number of the cases of "genuine croupous pneumonia" which were admitted to the Municipal Hospital at Cologne during the years 1879–1890, during both months of December and January, were as follows, taking the individual years: 1879–1890, 17; 1880–1881, 16; 1881–1882, 19; 1882–1883, 18; 1883–1884, 23; 1884–1885, 35; 1885–1886, 41; 1886–1887, 30; 1887–1888, 32; 1888–1889, 24. On the other hand, during December and January of 1889–1890, at the time of the influenza epidemic, there were 66 cases. These 66 cases of "genuine croupous pneumonia" occurring during the influenza months, December and January, of 1889–1890, are divided among the individual weeks as follows: December 1 to 10, 10 cases; December 11 to 20, 6 cases; December 21 to 31 (the height of the influenza epidemic), 24 cases; January 1 to 10, 16 cases; January 11 to 20, 6 cases; January 21 to 31, 4 cases.

"Genuine" croupous pneumonia was therefore most frequent exactly at the period when the influenza epidemic was at its height.†

According to Shattuck, the general mortality from pneumonia in Boston during the influenza months, December and January, 1889–1890, was double that of the preceding year.

Heryng observed in the Rochus Hospital at Warsaw, during the influenza period, six times as many cases of croupous pneumonia as in the corresponding period of other years.

A further proof that the cases of "primary genuine croupous pneumonia" which occurred with increased frequency during the time of influenza were due to influenza is seen in the fact that these "genuine" pneumonias often run an atypical course, both from a clinical and from a pathologic point of view, and, furthermore, were particularly malignant. In this respect they were like the clearly secondary croupous pneumonias, that is, those arising as a complication of influenza. P. Guttmann, Fürbringer, Landgraf, A. Vogl (Munich), Krannhals, Marchand, and many others called attention to the marked alteration in character of the "genuine croupous pneumonias" of influenza. We laid stress ourselves on this fact in our lectures of 1889. This fact, furthermore, shows and fully agrees with what was said above, that this presumed "genuine" croupous pneumonia of influenza periods is mostly not a genuine pneumonia, but one caused by influenza infection, that is, a mixed infection representing what we designated "the pneumonic form of influenza."

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* Week of the influenza epidemic.

† Regarding the details, compare with our influenza lectures (pp. 5 and 36–42), together with the corresponding instructive curves.

We will now briefly consider the croupous pneumonia caused by influenza. We will consider the clinical and pathologic characteristics together, as only in this way can a correct picture be obtained.

The fibrinous pneumonias occurring with influenza frequently differ markedly in their pathologic and clinical characteristics from the typical picture of genuine croupous pneumonia. The inflammatory areas are frequently only lobular (partially lobar) and only gradually become lobar. The pneumonia is often bilateral and is occasionally multiple. The infiltration not uncommonly forms a flabby, indistinctly granular hepatization. The lobar infiltrations occasionally still show the structure of lobular areas at various stages, in that in one and the same lobule there occur red and gray areas of hepatization side by side, but evidently of a granular character.

The stage of inflammatory engorgement often exists for some time before compact infiltration occurs (for this reason there are at first only relative dulness and permanent crepitations without bronchial breathing). The initial rigor is frequently absent, since the pneumonia gradually develops from the influenza. The fever-curve occasionally shows marked remissions and even intermissions corresponding to the progression, by stages, of these pneumonias. The typical rusty sputum is often absent, a purulent sputum taking its place, because the diffuse grippal bronchitis which exists at the same time causes so much purulent secretion that the pneumonic sputum is not apparent. The accompanying influenzal capillary bronchitis is characterized, frequently from the beginning, by dyspnea and cyanosis, which are quite disproportionate to the slight amount of the pneumonic infiltration. From the onset of the pneumonia there is marked weakness of the heart, with tachycardia and a small pulse. Resolution is rarely by crisis, but by lysis. Seropurulent or purulent pleural effusions frequently occur, occasionally even at the onset of the pneumonia, but usually at the height of the affection. We shall in the next section (Clinical Characteristics and Course of the Influenza Pneumonias) call attention to several other atypical characters of the pneumonia.

Nevertheless, in this description of atypical forms of croupous pneumonia in influenza we must not lose sight of the fact that the disease often runs the characteristic normal type (onset with chill, acute lobar infiltration, rusty sputum, crisis, etc.), and the typical picture of croupous pneumonia is also frequently found at the autopsy.

The above-mentioned clinical and pathologic characteristics of the croupous influenza pneumonia are by no means typical of this form alone. Pneumonia occurs in the very same manner, that is to say, with all the mentioned anomalies, as a primary disease, and has long been known by different names, *e. g.*: atypical, asthenic, týphoid malignant, contagious, and infectious pneumonia. It occurs commonly in the small epidemics or groups (house, family, prison epidemics), and frequently has a markedly contagious character. In an article,* now apparently forgotten, upon these asthenic pneumonias, as I called them at that time, I said, in the year 1874, therefore before the time of bacteriology, that these pneumonias were different from the ordinary croupous pneumonias, and were probably due to an infection with other, more malignant, causes of disease.

But upon the basis of further clinical, pathologic, and bacteriologic investigation I have, in the course of the last twenty years, arrived at a different opinion, that all these atypical pneumonias are only varieties of the endemic-epidemic croupous pneumonia resulting from a combination of its specific micro-organism with pyogenic cocci, especially streptococci. In this opinion I am strengthened by the fact, which I pointed out in 1874,† that during the time of such atypical epidemics, for example, in a malignant epidemic, one or more cases in a house or institution may run a normal course of croupous pneumonia, and a postmortem examination show the classic picture, including the diplococci of true croupous pneumonia.

The opinion which we hold regarding atypical croupous influenza pneumonia and primary atypical pneumonia is then as follows: Croupous pneumonia becomes atypical, asthenic, malignant, etc.—(1) By the combination of the specific cause of genuine pneumonia, either from the onset or in the course of the disease, with other cocci, generally with streptococci, to cause a mixed infection; this occurs at all times, frequently in small local epidemics. (2) By the combination of the specific cause of croupous pneumonia with the bacilli of influenza, primarily or secondarily, to produce a mixed infection. This occurs only when influenza coëxists. The clinical pathologic result of these etiologically different mixed infections is the same. In both cases the same manifold clinical pathologic deviations from the clinical picture of the pure genuine croupous pneumonia arise.

With the previously described forms, with the catarrhal bronchopneumonia, the fibrinous and the serofibrinous pneumonia, the varieties of inflammations of the lungs occurring in influenza are by no means exhausted. We must also call attention to a rare but clinically important form of pneumonia, which belongs to the previously mentioned variety of cellular pneumonia and is generally thus classified, but nevertheless, both clinically and pathologically, requires an individual description. This variety is by no means peculiar to influenza. It occurs frequently, as I pointed out long ago,* in other infectious diseases, such as scarlet fever, whooping-cough, measles, etc. In the following lines we will briefly discuss the most important clinical pathologic features of this variety of pneumonia.

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* "Upon Asthenic Pneumonias," "Volkmann's Sammlung klin. Vorträge," 1874, No. 82.

† *Loc. cit.*, pp. 30, 31.

It often arises acutely, like a croupous pneumonia, and attacks immediately a whole lobe, generally the upper lobe. Clinically, as we pointed out in our influenza lectures, it gives the impression of a croupous lobar pneumonia, until the postmortem examination discloses its true character. The cut surfaces of the lung are entirely smooth, homogeneous, of a fleshy red to a bluish-red color, of a fleshy, elastic consistence, and totally devoid of air. Neither fluid nor air can be expressed, nor do drops of pus flow from the severed bronchi. It is, as I have remarked in my lectures, a great error to assume that these acutely arising lobar infiltrations are formed by the confluence of lobular areas or result from an ordinary bronchopneumonia. They belong neither clinically nor pathologically to the latter. Histologically, the pneumonia is characterized by extreme vascularity. The alveolar septa are broad and the seat of round-cell infiltration; the lumina of the alveoli are filled with cells, but only traces of fibrin can be detected. The cells consist of a small number of red blood-cells, the larger number of leukocytes, but notably large epithelioid cells, which we believe to represent desquamated alveolar epithelium. This peculiarity differentiates it, from a purely histologic point of view, from the usual catarrhal pneumonia, which, on account of the large number of leukocytes, represents pus-formation "in optima forma," as Pfeiffer terms it. The acute lobar desquamative pneumonia described by Buhl, which has unjustly been forgotten, is clinically and pathologically almost identical with the form which we are now considering, namely, "the acute lobular cellular pneumonia." On account of the flesh-like consistence of the infiltrated lobe we have in the past (1882) used the expression "inflammatory carnification." We must, however, now withdraw this name, as Weichselbaum and Kundrat have lately used it to designate something quite different, namely, chronic indurative processes. Rusty sputum is never seen. The appearance of this sputum alone makes the differential diagnosis from croupous pneumonia possible; no other sign is absolutely pathognomonic. The form of pneumonia just described arises only secondarily in the course of influenza and other infectious diseases, such as scarlet fever, measles, whooping-cough, etc. It has absolutely nothing to do with the so-called "primary streptococcus pneumonia." Bacteriologically, divers other cocci are found, and, as usual, in all other kinds of inflammatory areas, especially streptococci. The presence of the influenza bacillus in this variety of pneumonia has not yet been demonstrated.

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* "Deutsch. med. Wochenschr.," 1882, p. 268.

We must also shortly describe another form, which was designated, both bacteriologically and pathologically, by Winkler as the most important and most frequent complication of influenza. It concerns a special class of pneumonic affections which the author described first in 1888 as "acute primary streptococcus pneumonia"—a pneumonia which, since that time, has persisted in Bonn. It is remarkable that whereas this pneumonia, before the influenza pandemic, occurred in particularly malignant endemics, "reminding one of typhus or septicemia," later, in the influenza period, when its similarity to influenza was astounding, it suddenly took on a milder character, and in the years 1893–1894 "these pneumonias suddenly became of short duration and not at all dangerous to life." Finkler thinks it likely that "in Bonn an endemic distribution of streptococci existed, so that before, during, and after influenza, streptococcus pneumonia became prevalent." In the influenza period there was in Bonn "a very remarkable epidemic, a mixed infection of influenza and acute primary streptococcus pneumonia."

According to Finkler, this primary streptococcus pneumonia has pathologically nothing in common "with croupous pneumonia," and it is not a bronchopneumonia, but occurs primarily in the lung, and is not necessarily preceded by bronchitis. It always arises in lobular, frequently multiple areas, which "only rarely give rise to pseudolobar forms of infiltration." "The cut surface of the lung is smooth, with no hepatization, but showing splenization." Microscopically, the infiltrated areas are "lobular areas showing the characters of an acute interstitial pneumonia, chiefly with a catarrhal exudation into the alveolar lumina, and but rarely accompanied by an admixture of fibrin; the alveoli are filled with fluid and with large and small epithelioid and round cells."

The lobular, catarrhal streptococcus pneumonia complicating influenza has been alluded to above. (See p. 611.) We emphasized the fact that in the course of a catarrhal pneumonia caused by the influenza bacillus streptococci might enter either simultaneously or secondarily, and finally even outnumber the influenza bacilli. The inflamed lung of influenza becomes the battlefield of various cocci, of which first one, and then the other, obtains the mastery. In a similar manner we may explain the fibrinous form of influenza pneumonia as a mixed or secondary infection with the Diplococcus lanceolatus.

The question concerning the primary or genuine streptococcus pneumonia (Finkler) is another matter. The confusion of this form with the streptococcus pneumonia depends upon mixed or secondary infections during the course of influenza, which has unnecessarily complicated a really simple question. This secondary streptococcus pneumonia is based upon sound pathologic or clinical data. Different, however, is the case with the primary form, which is supposed to occur as a nosologic entity, and to attack healthy individuals in a similar manner to a croupous pneumonia—suddenly with a rigor. In the course of time a marked change has taken place, during the prevalence of influenza, in this form of pneumonia—*i. e.*, it has changed from an originally malignant to a benign and harmless affection. Clinically and bacteriologically this malignant form corresponds to the well-known asthenic, typhoid or croupous pneumonia, whose atypical malignant character we have considered as due to a mixed streptococcal infection. (See p. 619.) But pathologically this primary streptococcus pneumonia is supposed to be of quite different nature, namely, an intense catarrhal or cellular pneumonia, which "has absolutely nothing to do with the croupous variety," and consequently has also nothing in common with our atypical croupous pneumonia, whose exudate is often poor in fibrin (flabby hepatization), and whose structure is not infrequently of the lobular variety.

Nevertheless, many statements of Finkler point to the close relationship of his streptococcus pneumonia with the atypical croupous form. Thus in one case the whole left lung within seventeen hours, and in another case the whole right side within twelve hours, became "rapidly" infiltrated and "splenized." The fact that on postmortem examination of such acute cases a granular surface was not found is easily explained by the short duration of the clinical course of the disease, which in the latter case existed only for twelve hours. The statement of Finkler that "rusty pneumonic sputa are by no means regularly found" signifies that such sputa, which are pathognomonic of the croupous form, were, at any rate, not uncommon.

For this "new class" of the primary streptococcus pneumonias the term "erysipelas of the lung," in use during the last century, has been proposed. In support of this designation the following points are brought forward: 1. "The pathologic character and the cellular nature of the inflammatory process," although this character is common to all catarrhal pneumonias. 2. "The marked disposition of continuous extension from lobule to lobule," which again is a peculiarity that is noticed in all bronchopneumonias and is by no means rare even in croupous pneumonia. 3. "The intense erysipelatous reddening and swelling of the trachea and bronchi," which also take place occasionally in all forms of pneumonia. 4. "That the disease is caused by the Streptococcus erysipelatis," but here again, to what confusion would it lead if we considered all processes in which streptococci were found as erysipelas? 5. "The character of the inflammation as an acute interstitial pneumonia"; in other places the inflammation is defined as "a predominantly cellular variety, with affection of the interstitial tissue."

Such interstitial processes, edematous swelling, granular infiltration, leukocytic accumulation in the interstices between the alveoli, as well as around the vessels and bronchi, are found in all forms of pneumonia, and especially in the catarrhal as well as in certain stages of croupous pneumonia.* The choice of the term "erysipelas of the lung" for the "new class of pneumonias" seemed to indicate that the most important pathologic characteristic of erysipelas, namely, the filling of the lymph-channels with streptococci, would be found, but of this we nowhere find any mention. All that we read of is the occasional "filling of the larger lymph-vessels with masses of coagulum."

We believe that we have, in the foregoing, conclusively shown that besides the true catarrhal influenza pneumonia, due to the bacillus of Pfeiffer and to the catarrhal streptococcic pneumonia, the fibrinous or cellular fibrinous, lobular and lobar pneumonia plays a considerable part as a complication or sequela of influenza.

If some physicians have observed only catarrhal pneumonia as the result of influenza, I can explain this remarkable statement only on the supposition that these observers regarded clinically every pneumonia as catarrhal, because they believed, on *a priori* grounds, that such was the only form of pneumonia occurring in influenza. The clinical course of croupous pneumonia occurring in influenza being frequently atypical, it was taken to be a catarrhal form, because of the "non-pneumonic," generally purulent sputum and the gradual, lobular consolidation. How is it possible, however, to understand that such persons did not notice croupous pneumonia in the course of influenza upon the postmortem table, and in this way have cleared up their mistakes? To explain this I can only suppose that these observers saw the croupous lobar and lobular pneumonias, but did not recognize their relation to influenza, and consequently considered them to be cases of primary genuine croupous pneumonia.

For the present, of course, we must account for the great frequency of the croupous and the cellular-croupous pneumonia in influenza by a mixed infection with the "cause of croupous pneumonia." Perhaps the time will come when the capability of the influenza bacillus to produce fibrinous inflammations of the lung will be proved. Speaking frankly, our present knowledge as to the "specific cause" of the different clinical pathologic forms of inflammation of the lung is still very uncertain and imperfect. Even the apparently well-substantiated position of the "Diplococcus pneumoniæ" as the cause of the endemic-epidemic disease, "croupous pneumonia," is by no means so certain as the majority of persons to-day believe. We need only mention the fact, which has been proved again and again, of the presence of streptococci only in croupous pneumonic infiltrations, of the exclusive presence of the Diplococcus pneumoniæ in the catarrhal pneumonia of measles (H. Neumann); further, that Kreibich (from the Pathologic Anatomic Institute in Vienna), among 27 lobular aspiration pneumonias, found the diplococcus of pneumonia 23 times, and of these, 11 times this germ alone.

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* Compare our influenza discourses, p. 44.

Only the combined activity of the clinician with the pathologist and bacteriologist will make it possible to clear up the vexed questions on which we have touched above.

We agree completely with the view which Wassermann (1893) has put forth in the following terms: "It would be premature to try at the present time to give a conclusive analysis of the inflammatory pulmonary affections on a basis of bacteriologic investigation. To arrive at this goal will require still much careful research in the laboratory as well as at the bedside. We are familiar at the present time with quite a number of parasites that are able to produce such disturbances; we know that just as the diplococcus of Fränkel, so also the influenza bacillus of Pfeiffer, the bacillus of Friedländer, streptococci, and staphylococci are able to produce inflammations of the lung. At any rate the number of causative factors which may produce inflammatory conditions in the lung is large, and it is very uncertain, even unlikely, that all the causes of inflammations of the lung are known to us at the present time."

CLINICAL ASPECT AND COURSE OF INFLUENZA PNEUMONIA.

The manner in which pneumonia develops in influenza varies. We have called attention to those cases where both diseases commence with a rigor, and called it the "pneumonic form of influenza." To this category belong the catarrhal as well as many of the true croupous inflammations. More frequently by far does pneumonia follow influenza. The development of pneumonia is then often insidious. High fever without chill, increasing dyspnea, intense cough, all show the exacerbation of the influenza process, and soon after a circumscribed inflammatory area in the lung reveals its existence by the presence of crepitations. In a large number of cases the pneumonia follows on an attack of influenza. One, two, or even more days later a relapse occurs, sometimes but not always with a rigor; the influenza manifestations seem to recrudesce, but in reality they are the first signs of the slowly developing pneumonia. Many so-called relapses depend upon this condition. In these cases the pneumonic attack often comes on the first time the influenza convalescent goes out; hence the universal view that the patient convalescing from influenza is very liable to catch cold and easily gets inflammation of the lungs.

While all symptoms—rigor, high fever, dyspnea, lancinating pain, and even the typical sputum—indicate the presence of pneumonia, it is sometimes impossible to locate it for several days. The first indications very often are noted in areas varying from the size of a silver dollar to that of a small plate, which, upon careful physical examination, are characterized by relative dulness, fine crepitant râles, subbronchial breathing, and weak bronchophony. I attach particular value to the last physical sign for facilitating the detection of small inflamed areas.

The pneumonic areas, both lobular and lobar, occasionally throughout the whole course of the pneumonia up to crisis or lysis, do not show absolute dulness and pure bronchial breathing, but for from six to eight days and even longer fine crepitant râles can be heard, together with only relative dulness and bronchophony (crepitatio permanens).

A very frequent characteristic of all forms of influenza pneumonia, the croupous variety not excepted, is the lobular commencement (that is, partially lobar), the gradual creeping character from lobule to lobule, and the frequent bilaterality of the pneumonia.

But from this lobular development of the infiltration we cannot at the bedside conclude that any pneumonia is of the catarrhal variety or a bronchopneumonia. Similar characteristics are not rarely present in the croupous forms.

Regarding the occurrence of such lobular croupous pneumonia in influenza there has been for a long time no doubt. We early called attention to this form. Birch-Hirschfeld has, as we have previously seen, divided croupous influenza pneumonia statistically into lobar and lobular forms. (Compare p. 613.) This is not peculiar to influenza. The rare croupous pneumonia of measles, diphtheria, and whooping-cough regularly shows a lobular structure. Strümpell especially mentions the "lobular croupous pneumonia" in measles, but even the every-day genuine lobar croupous pneumonia by no means always affects the entire lobe at one time. The pathologist most often sees the whole lobe affected, but cases are common in which, besides a completely infiltrated lobe, partly lobar or lobular fibrinous areas in other lobes are found postmortem. With the clinician who is able to note the course of genuine croupous pneumonia step by step it is a frequent experience that the genuine croupous pneumonia gradually and slowly makes its way over the entire lobe, affecting at first the dorsal portion, and the ventral part either much later or not at all, especially in apical pneumonia. The clinical form of pneumonia migrans ascendens and descendens frequently occurs in one and the same lobe of lung.

Of interest are those cases in which in the same lung, or even in the same lobe of a lung, fibrinous areas of a different age, red and gray hepatization, are found close together. Such a hepatized lobe shows very plainly the lobular composition of croupous pneumonia. In our influenza lectures we have called attention to some instances of this kind.*

> "Thus, for example in one case we found, in the center of the left lower lobe, which had undergone red hepatization, a wedge about the size of a lemon, of yellowish-gray color, and granular surface; a focus cut off by a perfectly sharp border from the surrounding red hepatized portion."

The remarkably slow development of croupous pneumonia in influenza is also shown by the fact that we occasionally find, when death takes place late (about the seventh day of pneumonia), the affected lobe in a condition of firm red hepatization. A. Vogl emphasizes the same fact.

> In one case affecting a young man aged twenty-two we performed the postmortem upon the ninth day of a double lobar croupous influenza pneumonia which was bilateral from the commencement. We expected, on account of the course and duration of the affection, to find gray hepatization, but were surprised to find a fresh, brownish-red hepatization of both lower lobes (microscopically, fibrinous pneumonia with marked hyperemia).†

On the other hand, occasionally a rapid change of croupous pneumonia into the stage of gray hepatization and mucopurulent softening is found. We have observed this as early as the third day of pneumonia. A. Vogl found, on the fourth day, "already purulent change of the fibrinous exudate." In reference to these cases we remarked in December, 1889: "the gray, mucopurulent softening of a hepatized lobe as early as the third day of pneumonia is a remarkable condition, and is probably due to the fact that croupous influenza pneumonia is often characterized from the beginning by a copious infiltration of leukocytes into the alveolar lumina and interstitial parts of the lung."

> "The lung of a patient dying of this affection on the ninth day of influenza, that is, on the fifth day of the pneumonia, showed a very remarkable picture. The left lower lobe was large; its pleura covered with a thin, fibrinous membrane; the lobe upon section showed a variegated surface, consisting of dark-red, flat infiltrates alternating with gray, markedly granular areas having the typical appearance of yellowish-gray hepatization. The dark-red areas were also devoid of air. The right lung was, with the exception of the upper part of the upper lobe and a small part of the anterior border, absolutely airless, infiltrated partly with red and smooth and partly gray-red and gray granular exu-

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* *Loc. cit.*, pp. 42, 43, and 50.

† Influenza lectures, p. 47.

dation. The right lower lobe on section showed a gray, granular surface. Therefore, here again we had gray hepatization upon the fifth day of pneumonia, with lobular mixed infiltrates of variable appearance."*

We must mention also the cases in which lobar influenza pneumonia runs a protracted course, so that, after the crisis has occurred, with a normal temperature or with the continuance of an intermittent or remittent fever, the lobar infiltration, with complete dulness and pure bronchial respiration, remains without redux crepitation and without râles for a week or even longer.

"With such slowly absorbed infiltrations, especially in the lower lobe, we have often been in doubt as to the diagnosis, whether an infiltration or an exudate were present, until the aspirating needle confirmed our assumption of the presence of an infiltration." In several cases of protracted pneumonia lasting for weeks with intermittent fever, especially with a hereditary history and when an upper lobe was the seat of the pneumonia, we suspected tuberculosis, until complete resolution removed the suspicion. In such cases of delayed resolution the purulent and blood-streaked sputum outlasted the acute stage of pneumonia.

Such influenza pneumonias are, as clinical and pathologic statistics† show, frequently multiple (in our statistics, 60 per cent. of the cases), and very often are also bilateral from the beginning. We emphasize the expression "from the beginning," for it is well known that a genuine croupous pneumonia may frequently migrate to the opposite side (pneumonia ascendens, descendens, saliens, migrans, cruciata). Occasionally in bilateral pneumonia the inflammation of one side would affect the whole lobe, while the other side remained lobular—that is, partially lobar—during the whole course.

The influenza double pneumonia occasionally was characterized by a remarkably rapid course and a rapid dissemination over several lobes. While such cases occur in ordinary times, they were particularly frequent during the influenza period. In our lectures we called attention to the cases of a boy nine years of age, of a girl eight years of age, and of a girl eighteen years of age who all died from asphyxia due to a croupous pneumonia, through infiltration of all the lobes.‡

On the other hand, there occurs not infrequently an abortive rudimentary pneumonia ("pneumonia fruste"); cases characterized by their acute nature, chill, sharp rise of temperature, lancinating pains, and dyspnea, with distinct signs of a lobular or lobar engorgement (crepitation) or also of a firm infiltration (bronchial breathing), and terminating in permanent resolution in from one to three days (pneumonia ephemera, biduana). As an example of such pneumonia we would refer to the following case, quoted in our lectures:

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* Influenza lectures, p. 50.

† Compare our influenza lectures, p. 38.

‡ *Loc. cit.*, p. 48.

"H. B., twenty-two years of age, was taken with a chill on December 21, 1889, together with all the symptoms of influenza. Moderate fever to December 24. On this day there were complete defervescence and euphoria. On December 25 renewed chill, with high temperature, rising to 40.7° C. Furious headache, with maniacal delirium. Marked dyspnea. Physical examination: Dulness with profuse fine crepitation, with some pleural friction during expiration. Bloody sputa. December 26 critical fall of temperature, sweating, entirely normal mental condition, and convalescence."

Many observers very correctly call attention to the numerous cases of influenza pneumonia characterized by an intermittent course, together with corresponding remittent or intermittent temperature curves (Landgraf). The cause of this condition is the successive involvement of the lobular inflammatory areas, and therefore occurs most frequently in bronchopneumonia, but by no means infrequently, and in a similar manner in croupous pneumonia.

Since the intervals between the individual attacks of pneumonia may be several days, we then have the picture of recurrent pneumonia, of which we gave examples in our lecture.*

F., twenty-three years of age, of robust appearance, was taken ill on December 8, 1889, with a chill and all the typical signs of influenza. Fever disappeared after two days, but the bronchial manifestations continued. On December 25 pain in the left side, high fever, without chill and dyspnea. In the right upper lobe (dorsal) and in the left lower lobe there were evident signs of engorgement (crepitation, subbronchial breathing, bronchophony). The infiltration in the dorsal portion of the right upper lobe was soon complete (dulness, bronchial breathing). On January 3 critical fall of temperature and all the signs of resolution. On January 4 and January 5 complete apyrexia. The dulness had disappeared; moist, moderately large bronchial râles were heard. On January 6 the temperature again rose, with a rigor, up to 40.5° C. The dorsal part of the right upper lobe was completely infiltrated anew. In place of the previous râles of resolution, bronchial breathing with complete dulness again appeared. This pneumonia ended by crisis upon the eighth day (January 14). But the purulent expectoration mixed with blood persisted for some time. Here we have the duration of a pneumonia recurrens of twenty-one days, including the period of intermission.

J. F., aged twenty-one, was taken ill upon the twenty-fourth of December, 1889, with typical influenza. Upon the twenty-sixth of December apyrexia with complete euphoria. On the twenty-eighth of December rigor, dyspnea, and at once purulent bloody sputum with yellow froth and much serum. In the right middle lobe and in the left lower lobe crepitations and relative dulness. Temperature, 39.8° to 40.6° C. Upon the thirtieth, complete apyrexia, but continuation of expectoration and dyspnea. Upon the thirty-first, relatively comfort-able. Upon the first of January, without a chill, a rise in the temperature to 40.3° C.; increased dyspnea; now a pneumonic area in the left upper lobe (at the apex and the surrounding areas) can be demonstrated. From the first to the third of January, high continued fever. Upon the fourth of January complete apyrexia; upon the fifth of January, rigor and a new area of inflammation in the supraspinal region of the left upper lobe was noticed. Upon the ninth of January critical fall of temperature; euphoria. The purulent sputum continued for two to three weeks longer. Recovery. We have here, in the period of thirteen days, three distinct attacks of pneumonia.

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* *Loc. cit.*, p. 48.

Influenza pneumonia occasionally shows a recurring character in the sense that the inflammatory process frequently changes its position at short intervals. Admitting that this occurrence is more characteristic of the catarrhal form, nevertheless it must be noted that such cases of pneumonia fugax are, as has been proved by autopsy, not infrequently of a fibrinous or cellular-fibrinous nature, and they also sometimes terminate, after several recurrences, as a lobar-croupous pneumonia.

Clinically, these successional pneumonias run an irregular course, both as regards the condition of the patients, who are better one day, worse the next, and also as regards the temperature, which is subject to steep ascents and as sudden falls. Teissier very rightly remarks: "Ces poussées se reproduisent souvent avec une persistance désespèrante, si bien, qu'en croit en avoir fini un jour de façon à pouvoir prédire une issue favorable, et le lendemain se produit une poussée nouvelle qui met les jours des malades en danger ou amène la mort d'une façon rapide."

We have still to call attention to some important acute affections of the lung which resemble pneumonia; first of all, those cases in which, either at the beginning or at the height of the attack of influenza, severe dyspnea and cyanosis with either high or only moderate temperature set in. On auscultation one finds, either scattered all over or limited to one side or lobe, marked crepitus without dulness. Expectoration may be absent, or there may be spumous or sanguinolent spumous sputum in large quantities, occasionally even pure bloody sputum, as if from an infarct. Such patients may die after a few days with the symptoms of marked cardiac asthenia and tachycardia. At the autopsy one finds neither a croupous nor a bronchopneumonia, but an enormous hyperemia of the lungs. Teissier and others call these acute, frequently fatal cases of hyperemia of the lung (we have already called attention to these under Acute Diffuse Capillary Bronchitis, compare p. 605) "congestion, pulmonarire, simple," or, on account of the hemoptysis occurring in such cases, as "congestion hæmoptoique" (Heryng). In accordance with an opinion especially in favor in France and England, Teissier, Althaus, and others consider this enormous hyperemia of the lungs to be due to a paresis of the pulmonary vasomotor nerves by the toxins of influenza.

Together with the hyperemia just described, an edema of the lungs, like the ordinary passive edema, which we often see in croupous pneumonia in the uninfiltrated lung (foaming edema, fluid containing air), exists. In other cases, besides the general hyperemia, there may be a localized edema of the lung or a lobe of quite a different character and importance. The affected lobe is large and heavy. It feels floppy; its cut surface is smooth, of a moist, mucoid appearance, and of a brown-red or gray-red color. The lobe is frequently almost devoid of air; the expressed edematous fluid is turbid and contains scarcely any air-bubbles. This condition is called "edematous infiltration," "infiltration pseudo-œdemateuse," or "serous pneumonia."

That this condition is really due to inflammatory processes ("inflammatory edema ") is shown by the fact that now and then in such an affected lobe several areas are found which have a firmer consistence and a more finely granular appearance (serofibrinous pneumonia), and also not infrequently the pleural covering of the affected lobe is cloudy and rough, and covered by a fine fibrinous membrane.

The sputum of influenza pneumonia in a majority of cases shows all those characteristics which we have already mentioned in describing influenza bronchitis, especially the copious serous, foamy sputum, often blood-streaked, and the purulent nummular sputum, or even sputum globosum. (Compare p. 605.) The latter is often present from the onset of the pneumonia; occasionally it is dotted or streaked with blood. From the purulent character of the sputum many observers were accustomed to diagnose a catarrhal pneumonia. This is certainly a mistake, for numerous cases, confirmed by autopsy, of croupous influenza pneumonia have taught us that the typical sputum croceum is but rarely found, the purely purulent sputum being far more common. This is due to the fact that the diffuse purulent influenza bronchitis accompanying the pneumonia decides the character of the expectoration and does not permit the pneumonic sputum croceum to make its appearance. This is well known in genuine croupous pneumonia attacking patients with chronic bronchitis and bronchorrhea, emphysema, bronchiectasis, etc.

The symptom-complex of influenza pneumonia is differentiated also in many other respects from typical pneumonia. The patient suffering from the combined diseases presents a composite picture.

The distinctive features are the general or papular redness of face, particularly on the forehead, nose, and around the eyes, the profuse sweating from the beginning of the attack, the spasmodic paroxysms of coughing peculiar to influenza; all these are symptoms which do not generally arise in a genuine pneumonia.

So far as the temperature is concerned, the fever-curve generally rises abruptly with the pneumonic attack, and remains at a high level. In a gradually developing pneumonia the rise of temperature also occasionally takes place gradually. The intermittent and recurring pneumonias previously alluded to have corresponding temperature-curves. The rise of temperature is frequently quite disproportionate to the extent of the pneumonia and the gravity of the attack.

TERMINATION OF THE INFLUENZA PNEUMONIA.

The termination of influenza pneumonia by a true crisis is unusual; resolution is often delayed for some time. Pseudocrises, viz., a fall of temperature lasting one or even several days, with subsequent exacerbations, frequently occur. This is true not only of the catarrhal variety, but also of the true croupous form.

Occasionally the compact lobar infiltration persists with total dulness and pure bronchial breathing without râles, or only with crepitation, and lasts much longer than in ordinary pneumonia. (Compare p. 627.)

But more frequently resolution of the lobar infiltration occurs, the percussion-note again becomes clear, while many, often metallic, coarse râles are heard over the whole lobe. Yet this condition does not improve: for weeks this same physical condition may persist; the sputum is purulent, often simulating the sputa occurring in tuberculosis, and occasionally containing blood; irregular, generally intermittent, occasionally "hectic" febrile fluctuations, with sweating accompany the process of delayed resolution; this is the protracted or "chronic influenza pneumonia." It is self-evident that when the process is situated in the upper lobe, there will be a strong suspicion of a possible tubercular affection, especially when we have to deal with weak individuals with hereditary taint or with such as have previously shown signs of tuberculosis. In such cases frequent examination of the expectoration for tubercle bacilli is of decisive importance. Graves called attention to the difficulty of differentiation between chronic influenza pneumonia and pulmonary tuberculosis in the epidemic of 1837, and at the same time pointed out the unusual frequency with which the upper lobes are affected in influenza pneumonia. Teissier, Chatin, and Collet classified these cases in a particular group of influenza, which they called "forme pseudo-phymique," and they describe many illustrative cases. These cases of protracted chronic influenza pneumonia sometimes terminate in the indurative condition described by Kundrat and Weichselbaum (indurative or chronic interstitial pneumonia). Nevertheless, it is well in practice not to assume prematurely the existence of this condition, since we know from numerous cases that after many weeks or even months resolution may take place. But in other cases there are permanent and slowly progressive changes terminating in chronic interstitial indurative pneumonia, with connective-tissue changes of large portions of the lung, and the formation of bronchiectatic cavities; and by the action of streptococci and staphylococci purulent necrotic and ulcerative processes may also occur.

We had the opportunity of observing two such cases from the time of the acute attack up to their fatal termination two years later.

Again and again the question of tubercle was discussed; the physical signs, the sputa, the temperature-curve, and the general appearance of the patient were all in its favor, but the entire absence of tubercle bacilli from the expectoration made us adhere to our diagnosis of chronic indurative and ulcerative pneumonia caused by influenza. The postmortem examination completely confirmed this diagnosis. It is true the lung had a certain amount of induration similar to a tubercular lung, but there were no tubercles, and the microscopic examination proved the absence of tuberculosis. Analogous cases, partly with and partly without postmortem examination, have been described by Teissier, Finkler, and Netter. The latter in a case lasting for fourteen months proved the influenzal nature of the chronic pneumonia by the constant finding of Pfeiffer's bacillus in the sputum and the absence of the tubercle bacillus. Pfeiffer, too, in such cases of chronic indurative pneumonia obtained the influenza bacilli in cover-glass preparations.

On the other hand, quite a number of cases occur in which true tuberculosis arises from the chronic influenza pneumonia. After the tubercle bacillus has been sought for in vain in the sputum for weeks it suddenly appears, and then the tubercular affection dominates the clinical situation until the case terminates. The question of Netter, "Must one not admit that grip can give rise to pulmonary tuberculosis?" has received an affirmative reply in a number of cases observed by us in which influenza has been followed by pulmonary tuberculosis. In most of such cases there may have been a latent tuberculosis, which the influenza attack, and particularly the pneumonia, enabled to manifest itself; in other cases the chronic grippal pneumonia may have prepared the soil for the tubercle bacilli.

The fact that influenza not rarely, and then generally by way of protracted pneumonia, leads to tuberculosis of the lungs, was known to the older writers and was emphasized by Fr. Hoffmann (1709), by Canstatt, Biermer, Lebert, Zülzer, and in our pandemic by Bouchard, A. Vogl, the German army reports, etc. R. Pfeiffer assumes that "the influenza pneumonia, when it affects lungs which have been previously affected by tubercle, may terminate directly in caseation."

A fact that has been substantiated by numerous observations contained in literature, as well as by statistics, is the frequency with which influenza pneumonia terminates in abscess formation and gangrene.

Weichselbaum and R. Pfeiffer, having described certain round-cell infiltrations in the peribronchial and intra-alveolar connective tissue, because associated with necrosis and purulent infiltration, as "smallest abscesses," it is not surprising that under similar conditions large abscesses occasionally arise ("purulent bronchopneumonia"). Ribbert, Marchand, and others also emphasize this tendency of influenza pneumonia to necrosis and abscess formation. But true croupous pneumonia also not seldom terminates in this manner. Zenker saw an abscess of the lung originate from a fibrinous pneumonia, and Rhyner's three cases of gangrene all developed from croupous pneumonia. In my influenza lectures of the spring of 1890 I reported five cases of abscess and two cases of gangrene of the lung following influenza pneumonia, and drew attention to the remarkable fact that all these seven cases occurred in juvenile individuals, the youngest being a boy of seven years. P. Guttmann, in postmortem examination of sixteen supposed genuine croupous pneumonia cases during the influenza epidemic, found large abscesses in two cases, this being a further proof of the correctness of our previous assertion that numerous cases of croupous influenza pneumonia were thought to be of the genuine variety. (Compare p. 617.)

In the pus from the abscesses diplococci, streptococci, and staphylococci were generally found. In one case P. Hitzig found the specific influenza bacillus.

We will not further consider the clinical signs of the abscess, the occasional perforation into a bronchus combined with copious evacuation of pus, and the consequent protracted indurative processes with cavity formation; neither will we consider the clinical and pathologic conditions of gangrene of the lung. It need hardly be mentioned that the latter occasionally ends fatally with severe hemorrhage or by perforation into the pleural cavity, giving rise to pneumothorax.

Nevertheless I should like briefly to mention two cases observed by me where, in healthy young individuals, sudden and complete pneumothorax of one side occurred at the height of the influenza attack, simultaneously with severe paroxysmal cough. A postmortem examination in both cases showed the condition of pulmonary hyperemia above described, but not a trace of pneumonia, still less gangrene, abscess, or even small necrotic areas. Even on inflating the totally collapsed lung the perforation could not be found. We must suppose that the tumultuous paroxysms of coughing, aided by the hyperemia of the lung, caused a vesicular or subpleural emphysema, and that the pneumothorax was due to the rupture of such an emphysematous vesicle. This was a pneumothorax, due, as its simple nature at the postmortem examination showed, to a pure and simple perforation of gas, as not infrequently occurs also in abscesses of the stomach, intestines, and appendix.

That influenza pneumonia may give rise to pneumothorax without gangrene or abscess formation by means of a circumscribed small pleural necrosis is shown by the observations of Mosler and Albu.

FREQUENCY OF PNEUMONIA IN INFLUENZA.

The extraordinarily large amount of statistical material which exists (P. Friedrich, F. Schmid, German collective investigations) is only of partial value. The usual percentage calculations are unreliable; in the first place, on account of the enormous number of mild influenza cases which do not come under the notice of the physicians, and also, as experience has proved, because numerous grippal pneumonias were erroneously classed as genuine. Unquestionably, more pneumonia of a slight and mild character occurs than is diagnosed clinically (latent pneumonia).

The frequency of inflammation of the lung in earlier epidemics has been estimated at from 5 to 10 per cent. (Biermer). In the official report in Bavaria the results vary in the different medical districts between 0.4 and 21 per cent., the average being 5 per cent. In the report from the Kingdom of Saxony the number varies between 0.5 and 15 per cent., the average being 7 per cent.; in Würtemberg, the same, 7 per cent. The German collective report (Litten) makes a careful investigation of this subject; it gives an average of from 6 to 8 per cent., and shows, apart from some large variations, a satisfactory agreement with the average pneumonia frequency in the separate German states and Prussian provinces. F. Schmid, in the Swiss official report, in a total of 3230 influenza cases, reports 93 pneumonias, or 2.8 per cent.

A well-classified outpatient material has unquestioned advantages. Fleischer, in Erlangen, notes that among 543 influenza patients there were only 3 cases of pneumonia, which would point to an unusually mild epidemic. On the other hand, Colley, in the Polyclinic at Greifswald, among 187 influenza patients saw 14 pneumonias, or 7 per cent. Gmeiner, physician to a glass factory in Bohemia, notes, in his carefully prepared statistics, that among 403 influenza patients, 90 pneumonias occurred, or 22 per cent., and that among these, 64 per cent. affected men, 14 per cent., women, and 21 per cent., children. According to our statistics, influenza pneumonia was more common among men than among women, a circumstance worthy of note, since genuine croupous pneumonia is certainly more common among men than among women.

According to the statistics of von Coler, the frequency of pneumonia in the Prussian army was extremely low. Among 34,556 patients, only 219 pneumonais occurred (0.6 per cent.), and in the complete army report (55,263 cases) 534 pneumonias (1 per cent.), and 175 cases of acute pleurisy (0.3 per cent.), are noted. In a girls' boarding-school in London, C. Bristowe reports, among 177 influenza patients, only 3 cases of pneumonia (1.7 per cent.). Hospital statistics, as a whole, naturally give a greater pneumonia frequency. In the Municipal Hospital at

Cologne it amounted to 24 per cent.; in the Hôtel Dieu, in the epidemic of 1837 (Copland), to 22 per cent.; in Friedrichshain (Berlin), to 22 per cent.; in Hamburg, to 17 per cent.; in Nuremberg, to 12 per cent.; in Freiburg (Bäumler), to 11.8 per cent.; in Riga (Krannhals), to 4 per cent.; in Munich, to 4 per cent.; in Leipsic (Jacob's Hospital), to 4 per cent.; in Magdeburg, to 3 per cent.

That pneumonia is the principal cause of death from influenza we have already noted in the section on Mortality. Of the numerous more detailed statistics in reference to this subject those of Carlsen, in Denmark, are especially noteworthy: Among 502 fatal cases of influenza, 273 were due to complications with pneumonia; 88 to other pulmonary and pleural affections; 49 to pulmonary phthisis; 33 to cerebral disease, while the remaining 59 are registered as simple influenza.

Even if we admit that, as regards the frequency of influenza pneumonia in the statistics of physicians, outpatient departments, and hospitals, chance has played a great part,—and to this cause the enormous variations are partly due,—we must, nevertheless, conclude (compare P. Friedrich's communications) that, as regards the frequency of grip pneumonia, locality unquestionably was an important factor; from several places it is even noted that pneumonia as a complication of influenza did not occur at all. If we wish to draw a conclusion from this statistically proved fact, we must admit that the influenza pneumonia due to mixed infection depended on temporary and local conditions. We content ourselves with the mere allusion to this important subject.

Numerous observers have expressed the opinion that pneumonia in the beginning of the epidemic of 1889 was rare, but became more frequent in the further course of influenza and toward the end of the influenza period. This increase may be apparent because, at the beginning of the epidemic, the complication was only partially or hardly at all recognized.

From our own statistical materials it would appear that the curve of frequency of influenza pneumonia ran parallel with that of the morbidity curve of influenza. There is an entire accord among German and English authors (Wutzdorff, Parsons, and others) that influenza pneumonia occurred much more frequently in the later epidemics than in the pandemic of 1889–1890. (Compare section on Mortality.)

As regards the danger to life from influenza pneumonia, we agree entirely with those numerous observers who consider this form of pneumonia to be more dangerous to life and its mortality considerably higher than that of the "genuine croupous pneumonia." The statistics, it is true, are not concordant. Occasionally they are even favorable; but they do not give a true picture, for the reason that numerous cases of pneumonia which ended fatally in the influenza period were erroneously counted as geniune pneumonias, and, therefore, were not counted as deaths due to influenza. The enormous statistical increase of the general mortality from pneumonia in the influenza period proves this. (Compare p. 568.)

The German collective report gave a mortality from influenza pneumonia of 17 per cent. (varying between 15 and 26 per cent.), a figure which is certainly not greater than the average mortality of genuine croupous pneumonia. In this question, however, hospital observations have a decided advantage, if merely on account of the control of diagnosis by autopsy. In the pandemic of 1889–1890 in the Municipal Hospital at Cologne, among 105 influenza pneumonias 32 terminated fatally, or 30 per cent. Krannhals, in his carefully prepared statistics for Riga in December, 1889, among the influenza pneumonias, records a mortality of 43.9 per cent. The pneumonia mortality in Boston varied in patients at different ages, and was between 29 and 45 per cent. (Mason).

AFFECTIONS OF THE PLEURA.

The pleura in the course of influenza is affected as a result of influenza pneumonia, which may be followed by a fibrinous, serous, or purulent pleurisy. Hemorrhagic exudates are exceedingly rare. But a primary pleurisy is by no means rare. Kundrat, on the basis of pathologic investigations, calls attention to a special peculiarity of influenza bronchitis "that, without pneumonic areas or pus-formation, purulent pleurisy frequently supervenes." The same condition is also mentioned by Kahler, Weichselbaum, Netter, Mayor, and others. R. Pfeiffer found, in two cases of empyema of the pleura, "enormous quantities of influenza bacilli in pure culture, and for the most part inclosed in the protoplasm of the pus-corpuscles; it is therefore proved that influenza bacilli can find their way to the surface of the lung, and may there give rise to a purulent exudate"; in three other cases of empyema following influenza the specific micro-organisms were not found. "They were replaced by streptococci or the diplococcus of Fränkel, and hence were due to a secondary infection." The bacteriologic etiology of this form of pleurisy is therefore quite clear.

Of great importance is an extraordinarily severe, usually fatal form of acute, primary influenza pleurisy, which may begin simultaneously with the influenza attack or more frequently develops upon the second or third day. This complication begins with a rigor and high continued fever; severe dyspnea and cyanosis set in early; in a short time a rapidly developing, often bilateral, very characteristic exudate is formed. The fluid is thin, opaque, and sero-purulent, of a peculiar pale yellow color; we have used the expression, "Weincrême-like"; by others (Fürbringer) this exudate has been appropriately named "mortar-like." By several autopsies we convinced ourselves* that these acute exudative grip pleurisies were primary—that is, apart from the diffuse severe bronchitis and hyperemia of the lung there was no inflammatory infiltration of the lungs. In the exudate, as we noted in our lectures in 1890, streptococci were frequently found in pure culture.

The complication of a diffuse, especially capillary, bronchitis or bronchopneumonia with pleural exudation, even in a slight amount, produces severe dyspnea, cyanosis, and marked cardiac asthenia. Even robust young individuals may be carried off in this manner within a few days, as the cases reported by us and A. Vogl (Munich) show.

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* *Loc. cit.*, pp. 4 and 57.

Gerhardt, Curschmann, and Heubner very properly called attention to the frequency of pleurisy complicating influenza pneumonia. Auerbach remarks. "These dry pleurisies are frequently distributed over the entire surface of the lung." Among the pathologists, Zahn called attention to the "extraordinarily frequent pleural exudates in catarrhal influenza pneumonia, which in the ordinary catarrhal pneumonia is rare." The German collective report agrees well with this statement. Among the 3185 observers, not less than 869 (or 27 per cent.) called special attention to pleurisy unaccompanied by pneumonia as a sequela of influenza (Fr. Stricker).

TUBERCULOSIS OF THE LUNGS AND INFLUENZA.

The mortality tables of all countries agree in showing considerable rise in the mortality from pulmonary tuberculosis in influenza periods. With this fact the observation of every clinician agrees,* that the course of tuberculosis of the lungs is markedly and unfavorably influenced by influenza and its pneumonic complications. Latent quiescent cases of tuberculosis became active; "healed" or healing foci broke out anew; afebrile cases were changed to the hectic type or to cases of acute "phthisis florida," and frequently hemoptysis was induced. The influenza bacillus, as Pfeiffer has remarked, prepares the way for a further invasion of the lungs by the tubercle bacillus. The same author found that the lungs of tuberculous patients form an especially favorable influenza soil, so that they grow and multiply on it for weeks and months; this has been termed the "chronic influenza of tuberculous patients." Nevertheless numerous phthisical patients have recovered not only from simple uncomplicated influenza, but also from influenza complicated by lobular and lobar pneumonia, as easily as other patients. Two facts are worthy of special note, namely: (1) That advanced phthisis, which, as a rule, gives a considerable degree of immunity toward acute infectious diseases, did not confer any immunity against influenza; and (2) that even advanced phthisical patients affected by influenza not rarely acquired lobar croupous pneumonia, which, apart from the presence of influenza, is extremely rare in phthisis.†

It was often asserted that phthisical patients showed special predisposition to influenza; Pfeiffer's results, just quoted, lend color to this view. H. Rieder has represented me as its chief exponent, but incorrectly, because already in my lectures of 1890 I said that "the figures available to support this view are too few for such a conclusion." The greatly increased death-rate from tuberculosis in influenza periods merely indicates a higher mortality, not a higher morbidity.

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* Compare P. Friedrich's instructive tables, *loc. cit.*, p. 197.

† Influenza lectures, *loc. cit.*, p. 53.

NERVOUS SYMPTOMS.

After the respiratory system, the nervous system is most frequently affected in influenza.

We have to deal only in part with gross anatomic inflammatory processes; more often with so-called functional disturbances of the motor, sensory, or vasomotor centers and tracts, and, finally, with the cortex of the cerebrum as the organ of consciousness and psychic functions.

Whereas the inflammatory phenomena (meningitis, encephalitis, myelitis) are attributed to the invasion of the influenza bacilli or of the microbes associated with them, the cause of the functional disturbances is usually assigned to the toxins produced by these microorganisms. But there can be no doubt that the toxins of influenza, which in our lectures (1889) we designated as "intense nerve poisons," are capable in themselves of producing inflammatory and degenerative changes, especially in the peripheral nerves, changes analogous to those produced by other bacterial toxins and poisons (alcohol, lead, mercury, etc.). It would mean writing a voluminous monograph if we tried to mention everything which has been observed in the older and especially in the newer literature in regard to nervous sequelæ and effects of influenza. These cases present complicated and unusual clinical pictures of varying combinations of paralyses, irritative motor phenomena, and various forms of anesthesia and hyperesthesia, atypical pictures of disease not admitting of classification, and whose description would require a detailed report of histories of all the special cases.

We cannot here enter into any critique of the various nervous diseases connected with influenza. When, as a sequel to influenza, there develop typical tabes dorsalis, paralysis agitans, spastic spinal paralysis, disseminated sclerosis, Graves' disease, or progressive paralysis, the most natural conclusion is to consider influenza as an intercurrent disease, which caused an already incipient but unnoticed affection to develop more rapidly than would have been the case without the occurrence of influenza. With a disease like influenza, which affects 50 per cent. of the population, it is certain that numerous nervous and other diseases which occur during the course or after the epidemic will be attributed, directly or indirectly, to influenza, although they would doubtlessly have appeared sooner or later in any case. Nevertheless, there can be no doubt that influenza has been the direct cause of numerous polymorphic diseases of the nervous system. The latest influenza pandemic and its recurrences have taught us something quite new in neurology, namely, an acute infectious disease, which, compared with all others, is characterized by its striking neurotoxic effects. The sentence on which we laid especial emphasis in our lectures (1889–1890)—"The influenza toxins are intense nervous poisons"—has found full justification in the history of earlier as well as in the latest epidemics.

Space will not allow us to quote all the authors who have described affections of the nervous system in influenza. But their observations in combination with our own form the basis of what follows.

AFFECTIONS OF THE SENSORY NERVES.

Among the neuralgias, headache is the most frequent attendant of influenza. It has its seat especially in the frontal and supra-orbital regions, at the back of the orbit; frequently also it affects the temporal and occipital regions, or again may be evenly distributed over the entire head. The pains ("douleur de tête cruelle," Saillant) are often very intense, so that the patients moan or rave (cephalæa agitata) or sit silently with their head tightly clasped with both hands (cephalæa attonita).

Occasionally a distinct obtusion of the senses occurs,—a sort of pain stupor,—or the picture of the disease may remind one of meningitis. Besides the cephalalgia, there are frequently pains in the back and lumbar region, intercostal neuralgia, pains in the lower extremities, especially in the knees and calves; furthermore, sciatica and diverse arthralgias. These neuralgias often persist into convalescence and even become chronic. This is especially true of trigeminal neuralgia and of the sciatic, intercostal, and dorsal nerves.

Certain chronic, sharply defined, post-influenzal neuralgias are designated as mastodynia, sternodynia, xiphodynia, chondrodynia, costodynia, sacrodynia, cystodynia, coccygodynia, achillodynia. Obstinate odontalgia and otalgia of purely nervous origin were observed already in the older epidemics. There is scarcely a sensory nerve that is not occasionally, at the height or in the course of influenza, the origin of severe neuralgia.

Some authors—*e. g.*, Stintzing, Bristowe, Preston—have statistically arranged the seat of the various neuralgias. In all these statistics cephalalgia naturally prevails with nearly 100 per cent.

Intercostal neuralgias with herpes zoster have been described by Kinnicutt, Edgren, Brakenridge, and by us. Joffroy reports six cases of severe neuralgia, picking out the nerves to the upper arm and shoulder, followed by atrophy of the deltoid, supraspinatus, and infraspinatus, pectoralis, and biceps. These were evidently cases of neuralgia due to neuritis (see below).

We must omit the muscular neuralgias (myalgias). They occur in various groups of muscles, frequently in several together, especially in the back, thigh, and calf, which are then often very painful on pressure. Patients frequently describe these pains as especially agonizing, and use comparisons, such as that "the muscles appear to be cut through by knives," or that they seem to be "drawn out of the body with burning hooks."

The influenza neuralgias and myalgias are characterized by periodic exacerbations, especially at night.

Finally we must call attention to the general hyperesthesia of the organs of sense, and especially of the skin. The latter is often painful to pressure, or even to touch, very much as in meningitis. In close relation to neuralgia and hyperesthesia are the peculiarly localized anesthesia and paresthesia of the cutaneous nerves.

We would especially mention a case described by us of total anesthesia of the second division of the fifth nerve. Here also belong anesthesia and paresthesia occurring in the course of the nerves of smell and taste. Cases of complete loss of the sense of taste are mentioned by Ash (1836), Senator, Leichtenstern, Fry; on one side only by S. Laache; loss of the sense of smell by Leichtenstern, Zwaardemaker; finally, peculiar parosmia by Barth and Dippe. Some of these phenomena were found in the epidemic of 1410 (Pasquier). Complete loss of the sense of smell and taste is noted by English authors in the epidemic of 1800.

PARALYSES DUE TO NEURITIS.

A glance at the great number of motor paralyses following influenza teaches us that they are due partly to neuritis, partly to cerebral or spinal implication.

In the group of paralyses due to neuritis, the influenza polyneuritis, the analogue of diphtheric paralysis, and that following other acute infectious diseases,—that is, a multiple degenerative neuritis,—is of chief importance. It is regarded as being due to the action of the specific toxins. The clinical picture varies with the distribution and extent of the nerve-tracts affected. Thus a fulminant polyneuritis may produce the complete clinical picture of an acute ascending, so-called Landry's paralysis, as in the cases described by Kahler and Eisenlohr. Neuritis of the extremities, especially of the lower extremities, sometimes leads to marked ataxia. This is the same curable acute "neuritic ataxia" of Strümpell which occurs occasionally in the course of other acute infectious diseases.

The prognosis of influenza polyneuritis appears to be better than that due to diphtheria; so far as I am aware, there is no published case in which the neuritis attacked the respiratory nerves and caused a fatal termination.

The numerous reports of cases show that polyneuritis due to influenza is no rare occurrence. We may mention the observations of Bidon, Brosset, Bruns, A. Church, Drasche, Holmberg, Homen, Jolly, Kahler, Krannhals, Leichtenstern, Leyden, Lojacone, Putnam, Remak, Ruhemann, Senator, Testi, Thue, Westphal.

The cases reported by Joffroy (see above), of paralysis due to neuritis, as also a case quoted by Bossers of paralysis of all four extremities, are remarkable inasmuch as the neuritis, besides affecting the motor tracts, also produced severe neuralgia in the sensory tracts. Remak also notes in his case of polyneuritis the presence of "slight sensory disturbances."

Frequently influenza neuritis is localized to single nerves and thus produces isolated or grouped paralyses. There are numerous observations which must be interpreted as dependent upon neuritis. Other observations are probably to be explained as resulting from circumscribed, partial, functional, or degenerative changes due to the influence of a toxin in the motor nuclei of the middle and fourth ventricle—so-called nuclear paralyses. This is especially the case in certain combined paralyses of the muscles of the eye, of the soft palate, and the pharynx, viz., muscle-groups which, being synergic, are innervated from the same nuclei. The course of these paralyses was without exception favorable, consequently the observations on them are entirely clinical. They relate to clinical pictures which exhibit a kaleidoscopic variety. As regards the pathologic basis of these symptoms, whether neuritic or nuclear, whether functional or toxic, or due to inflammatory degenerative changes in the nerves or nuclei, there is no evidence. But one fact may be regarded as certain in all the cases belonging to this group, namely, that there cannot be gross pathologic changes; the complete absence of all severe cerebrobulbar or spinal symptoms in these cases at once negatives such a supposition.

The following observations may be cited from the large amount of available material.

We meet with numerous reports of paralysis of the soft palate and muscles of the pharynx, with or without simultaneous paralysis of accommodation. They are completely analogous to those paralyses which so frequently occur after diphtheria. However, the clinical pictures produced by influenza neuritis are much more varied as regards the arrangement of special muscle groups affected by the paralysis, whereas the diphtheric scheme is more even and uniform. Influenza affords a greater and more minute selection of individual nerves and nerve nuclei. Hence rare forms of paralyses occur—for instance, bilateral trochlear paralysis (Pflüger), isolated paralysis of the superior rectus (Vallude), etc. We may add the following observations: Isolated paralysis of the soft palate (Heymann); paralysis of accommodation with or without paralysis of the soft palate and muscles of the pharynx (Joachim, Jankau, Pflüger, Uhthoff, Albrand, Stower, Greff, Bergmeister, Sattler, Landolt, Frank, Guttmann, Bock, Neumann); intermittent paralysis of accommodation (Uhthoff); paresis of the internal rectus (Pflüger); weakness of the internal recti (Frank, Königstein); paralysis of the superior rectus (Vallude); of both fourth nerves (Pflüger); of the third nerve (Fukala); of one or of both abducentes (Sattler, Coppez, van der Bergh); unilateral mydriasis (Lépine); bilateral paralysis of the third, fourth, and sixth nerves (Sattler, Pflüger); nuclear paralysis of the muscles of the eye—"polioencephalitis superior" (Pflüger, Guttmann, Goldflamm, Uhthoff, Schirmer). Further: Unilateral paralysis of the hypoglossal, with or without hemiatrophy of the tongue (Leyden, Flatten); paralysis of one recurrent laryngeal nerve (Trakauer); nuclear bulbar paralysis (Remak, Stembo, Guément, Fiessinger, Swiss report). Finally, isolated paralysis of one facial nerve without otitis (Laache); complete paralysis of one arm (Henoch, Bernhardt); atrophic paralysis in the distribution of certain shoulder, pectoral, and upper-arm nerves, of the deltoid, supraspinatus, and infraspinatus, trapezius, serratus pectoralis—"the scapulohumeral type" (Teissier, Joffroy).

We may include as belonging to neuritis isolated reports of single or combined paralyses of the radial, ulnar, and median nerves (Draper and German army report) and individual nerves of the lower extremity, the peroneal, tibial, and crural; also some monoplegias and paraplegias occurring during convalescence without any alarming symptoms of cerebrospinal disease (Henoch, Barhdt, Warfvinge, Riener), which may be most easily explained as the paralyses due to neuritis.

The paralyses due to neuritis and nuclear affections arise almost exclusively after influenza has run its course, frequently even a few weeks after, just like many similar postdiphtheric paralyses.

THE INFLUENZA ENCEPHALITIS.

A second important group of paralyses in influenza is of cerebral origin. These paralyses, hemiplegias and monoplegias, are clinically differentiated from the above-mentioned neuritic and nuclear varieties by their sudden apoplectiform onset, either at the very beginning or at the height of the influenza attack, with high fever and grave cerebral symptoms (delirium, early unconsciousness, coma, epileptiform convulsions, Jacksonian epilepsy, etc.). The clinical picture so frequently resembles apoplexy caused by cerebral hemorrhage or embolism accompanied by the hemiplegia that only the youth of the patient, the acute onset with rigors, the accompanying high fever, and the occurrence of such cases at the time of an influenza epidemic admit of differentiation from ordinary apoplexy. The differential diagnosis from ordinary apoplexy is easier if the influenza attack does not set in with the cerebral symptom-complex described above, but typical manifestations of influenza precede the cerebral symptoms by one or more days.

In exceptional cases this apoplectiform attack may develop suddenly during convalescence from influenza, with a renewed rigor and high fever. These cases we regard as influenza relapses, with the difference, however, that the second attack appears in the form of an influenza encephalitis.

Cerebral apoplexy has been described as a symptom of influenza in England as far back as the epidemic of 1743, and in 1782 by Michell (Holland), by Bodel in 1800 (Dordrecht), and in 1833 by Escherich and D. Lombard (Geneva). The latter observer in particular called attention to the cases of "cephalalgia with hemiplegia"; so, too, Fife in the epidemic of 1837. All these observations, however, and particularly the erroneously quoted cases of Récamier (1837) concerning "apoplectiform influenza," have been so vaguely described that it is impossible to make an exact diagnosis. There are no accounts of any postmortem examinations in this period.

Another statistical note regarding the most recent epidemic may be mentioned. The general mortality statistics concerning the frequency of apoplexy in England and Germany show that there was no increase of this condition during the period of influenza in these countries, which is not surprising since influenza apoplexy is always exceedingly uncommon and must be regarded as a rarity. On the other hand, the Swiss statistics of F. Schmid, tabulated during the principal epidemic month, January, 1890, show well a remarkable increase of mortality from "stroke."

In my influenza lectures of the spring of 1890 I first called attention to these apoplectiform hemiplegias and monoplegias occurring in influenza, and at that time reported no fewer than eight cases.* Some of these cases terminated fatally, others recovered.

Anatomically, there was neither simple cerebral hemorrhage nor an extensive embolus or thrombus, but a focal "acute hemorrhagic encephalitis" which up to that time had not been described. In the first case the foci were situated principally in the cerebral cortex, and in the later cases frequently also in the central ganglia and particularly in the thalamus. Regarding its pathogenesis, I conjectured at that time (1890) that "the condition consisted of foci of capillary emboli due probably to a dissemination of the influenza germs," an opinion which later on was substantiated by the demonstration of the specific organism in these encephalitic areas (Pfuhl, and especially Nauwerck).*

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* *Loc. cit.*, p. 29.

At the same time I pointed out that this variety of encephalitis is by no means pathognomonic of influenza. Such hemorrhagic encephalitic areas Klebs and I have observed occasionally in epidemic cerebrospinal meningitis during the epidemic of 1885–1886, in which cases these areas caused the hemiplegia which occurred in the course of the meningitis. Similar forms are occasionally met with in ulcerative endocarditis, and are doubtlessly due to capillary emboli.

During the years following the pandemic of 1889 we observed four more cases of acute hemorrhagic encephalitis, which were described by me,† and more exhaustively by Bücklers.‡ In the absence of marked influenza symptoms and because they did not occur during the epidemic we did not venture to attribute these cases with certainty to influenza. I classed them pathologically with the disease described by Strümpell in October, 1890, under the title, "Primary Acute Encephalitis." Undoubtedly these "primary" cases are to be attributed to microparasitic infection and the formation of emboli by unknown microbes.

Our observations regarding acute hemorrhagic grippal encephalitis were corroborated by the case described by Virchow-Senator, and especially by the reports of Fürbringer, Königsdorf, and J. Schmidt, and the domain of "primary acute encephalitis" was extended further by H. Oppenheim.

We cannot discuss more in detail the pathologic anatomy of this acute encephalitis that so frequently sets in with apoplectiform manifestations. The foci are usually sharply defined, varying in size from that of a cherry-stone to the size of a pigeon's egg; by the confluence of adjacent foci still larger areas may form. Sometimes only one area exists, but more frequently there are several (multiple encephalitis). It is nearly always situated in the gray matter, most frequently in the cerebral cortex and the central ganglia, and far less commonly in the pons and cerebellum. The encephalitic areas occasionally form wedges extending from the cerebral cortex or the central ganglia into the white matter of the hemispheres. Even in our earliest publication we called attention to the symmetric localization of the areas in both cerebral hemispheres. The encephalitic area in its typical form consists of innumerable dense aggregations of, as we expressed it, "flea-bite-like" dots of blood, between which the tissue is softened and of a gray to a grayish-red color. By secondary hemorrhage into the softened center larger hemorrhagic areas may arise. Undoubtedly such "cerebral hemorrhages" in influenza have been regarded as primary apoplexies, while the true condition was secondary hemorrhage into the softened central encephalitic area.

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* Compare the section on Bacteriology of Influenza, p. 585.

† "Deutsch. med. Wochenschr.," 1892, No. 2.

‡ "Arch. f. Psychiatrie und Nervenkrankh.," 1892, Bd. xxiv.

The veins in the areas of hemorrhagic encephalitis occasionally become the seat of thrombi; the thrombus may then extend further into the superior cerebral veins and the longitudinal sinus, or from the veins of the corpus striatum and the optic thalamus into the choroidal veins, the vena magna Galeni, the straight and transverse sinuses. In such cases the differentiation between primary encephalitis or primary thrombosis with secondary hemorrhagic softening is only possible upon microscopic examination. Occasionally hemorrhagic leptomeningitis and pachymeningitis are combined with influenzal encephalitis; in rare cases streaks of purulent exudate extending along the pial vessels are found. Undoubtedly the process, when the inflammation is not very intense and affects only small areas, may undergo resolution. Several of our acute cerebral influenza hemiplegias recovered in a very short time. Whether they were actually encephalitis is always uncertain in such cases. In no instance was there a permanent paralysis with contractions similar to that following ordinary apoplexies. Neither have such cases come under our notice in the literature. But the course of the illness is not always so tumultuous or so definitely apoplectiform as we have noted in describing the typical condition. The encephalitic hemiplegia in exceptional cases develops gradually, insidiously, and without such acute cerebral symptoms, although dizziness and headache, disturbances of consciousness with epileptiform convulsions, or even somnolence and coma, are usually frequent.

It is obvious that the symptoms vary markedly according to the intensity of the process, the number and size and especially the position of the inflamed areas. As regards the focal symptoms, there may be either complete hemiplegia, pure aphasia without motor disturbances, or only paralysis of individual nerves, like the facial, hypoglossal and brachial monoplegia, or, more rarely, crural monoplegia.

The process occurs especially in the motor cortex as small, sharply defined foci, whence the monoplegia. On the other hand, no authentic case is known of acute influenzal encephalitis, situate on the floor of the third or fourth ventricle, and giving rise to an acute hemorrhagic superior or inferior polioencephalitis.* All the reported cases of nuclear oculomotor paralysis developed after influenza had run its course, generally some time after, without fever or marked cerebral manifestations; in other words, they were typical cases of degenerative neuritis and neuronucleitis.

If the influenzal encephalitis spares the motor centers and tracts, it may run its course without any motor or paralytic symptoms. In one such case in which there were high fever and early unconsciousness, followed by death during coma, we discovered inflamed areas at the apex of both frontal lobes and the right temporal lobe.

Posthemiplegic motor disturbances, unilateral tremor, hemiataxia, hemichorea, and hemiparalysis agitans but rarely succeed influenza hemiplegia. Permanent paralyses followed by contractures, as previously mentioned, we have never seen.

Of course we do not go so far as to assume that all or even the greater part of the cerebral hemiplegias and monoplegias observed in influenza are caused by encephalitis. Very often other processes, *e. g.*, small extravasations of blood, emboli, and thrombi, may have occurred or transitory toxic influences on certain cerebral centers, or conditions of cerebral hyperemia, produced these results (Helweg, Kohts).

The cases of Erlenmeyer (Jacksonian epilepsy with unconsciousness and convulsions in the left arm), those of R. Gross (apoplectiform hemiplegias with or without aphasia and recovery already in twenty-four to forty-eight hours), the cases of Eichhorst, Stembo (motor aphasia with brachial hemiplegia), those of Remak (brachial monoplegia with anesthesia), those of Drasche (brachial monoplegia), those of Bilhaut (cortical epilepsy), of Prentis (three cases of postinfluenzal cerebral apoplexy), the cases of Herzfeld (left-sided hemiplegia with paralysis of the abducens, pupillary immobility, nystagmus, and aphasia), of Warfvinge,—(1) hemiparesis, followed by chorea; (2) hemiplegia with aphasia; (3) Jacksonian epilepsy, with fatal termination by excessive increase of the attacks,—and finally the cases of "isolated motor aphasia without paralytic symptoms" described by Brakenridge, Warfvinge, and Goudet, may have had different causes from encephalitis and may in part have been due (especially the last-described anatomic changes) to neuritis.† On the other hand, the case described by Revilliod as "cerebellitis," with softening, and also a well-described case by Dück

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* Compare, furthermore, p. 647, the case of Macdonald.

† Compare section on Neuritis, p. 640.

(Rimpar), may, without doubt, be attributed to hemorrhagic encephalitis. An observation made by Kohts, as he himself surmises, and perhaps also the case of Macdonald, described as a capillary hemorrhagic inferior polioencephalitis, fall into this category. Also Jennings' case (meningeal hemorrhage, hemorrhagic area of softening in the left temporal and frontal lobes) may be classified under encephalitis. Both of the cases observed by Straumann (fever, coma, death) may be most readily classified under the above-described form of "acute encephalitis without motor manifestations or motor paralysis."

The proof of the existence of an "acute focal hemorrhagic influenza encephalitis" in our most recent epidemics may be considered an advance in the pathology and anatomy of influenza, especially since Nauwerck and Pfuhl have added to these clinical observations by demonstrating the presence of the influenza bacilli in these areas.

We still must consider two other inflammatory cerebral affections caused by influenza.

Purulent encephalitis, abscess of the brain, frequently accompanied by purulent meningitis, most frequently arise from a purulent otitis, from suppurative processes in the accessory sinuses of the nose, in the frontal sinus (Redtenbacher), and from the antrum of Highmore. Pulmonary abscesses, pleural empyema, and, as Arzel believed in one case, purulent bronchitis and influenzal tonsillitis, may give rise to metastatic suppurating areas in the brain.

Influenza may also give rise to a primary purulent encephalitis (Bristowe, Leichtenstern, German army reports); and the mostly non-purulent hemorrhagic encephalitis may, under certain conditions, result in suppuration. Such a mixed form of hemorrhagic purulent encephalitis is seen in the case of Senator-Virchow. Abscess of the brain as a direct consequence of infection by the influenza bacilli has been proved by the detection of the specific organism in the pus by Pfuhl. That this bacillus possesses pyogenic properties and can give rise to an abscess through necrotic action upon the tissue is seen in the fact that the organism is capable by itself of bringing about suppuration in the most typical manner (R. Pfeiffer) in catarrhal pneumonia and in abscess of the lung, without mixed infection with the common pyogenic cocci.

INFLUENZA MENINGITIS.

We will pass over the cases in which an influenzal otitis or an empyema of the accessory cavities of the nose gives rise to a secondary purulent meningitis (Ewald, Bäumler). Of much more importance is the primary fulminating influenzal meningitis occurring at the height, or as a rule at the very beginning, of the influenza attack. We may term it the meningitic form of influenza. The specific bacilli probably enter into the cranial cavity from their primary focus, the nasal cavity, through the lymph-channels communicating with the subarachnoidal space, a phenomenon which is supposed by many to account for the transmission of epidemic cerebrospinal meningitis. But the germs can probably also be disseminated by the blood-channels. In the pus of suppurative meningitis there are mostly only the ordinary pyogenic cocci and the ubiquitous diplococcus lanceolatus to be found, but Pfuhl and Högerstedt have also found the specific influenza bacilli.

[In the case mentioned above of general influenzal infection, the bacillus of influenza was found in the cerebrospinal fluid and the cerebral abscesses, as well as in the blood. E. Fränkel also found only Bacillus influenzæ in two cases of meningitis.—Ed.]

Such cases of primary purulent influenzal meningitis have been described by Fürbringer, Kelsch and Antony, Maillart, Rendu, Kuskow, Revilliod, Mackay, Götz, Pel, Lennmalm, Edgren, and Köster. In our lectures of 1890 we reported four such highly acute fatal cases, together with the postmortem examination. The relation of the basal to the superficial meningitis in our cases was 1: 3.

In very acute influenzal meningitis, just like in the fulminating cases of epidemic cerebrospinal meningitis, there may be no macroscopic evidence of pus, while, on the other hand, there may be occasionally a copious purulent exudate, with no less acute course of the affection.

The manifestations vary according to whether the convexity of the brain, as is the rule (intense headache, early stupor, the rigidity of the neck), or the base of the brain is affected. In the latter case the differentiation between influenzal and epidemic cerebrospinal meningitis is often impossible, for both begin suddenly with chill and high fever, and cervical rigidity sets in at once; in both, herpes labialis is seen, although this is far more frequent in epidemic than in influenzal meningitis.

The certain diagnosis of epidemic meningitis, as a recent case of ours illustrated, can be established only by the demonstration of the highly characteristic specific Meningococcus intracellularis (Weichselbaum, Jäger) in the cerebrospinal fluid obtained by lumbar puncture. The influenza bacillus has not yet been found in the fluid obtained by lumbar puncture, nor has it or the Diplococcus intracellularis been found in the contents of the herpetic vesicles.

The differential diagnosis between influenza meningitis and epidemic cerebrospinal meningitis is easy when the influenza meningitis is accompanied or ushered in by the typical symptoms of influenza, that is, by coryza or diffuse bronchitis, or when pneumonia associates itself with the process; for such manifestations as were taught us by the epidemic of 1885–1886 never occur in true epidemic cerebrospinal meningitis. More especially, we never met with secondary pneumonia in this affection.* On the other hand, a differential diagnosis between cases of pneumonic meningitis in those in which the meningitis arises first and the pneumonia follows, and an influenzal meningitis with the same manifestations, is hardly possible. Of course, the demonstration of the influenza bacillus in the sputum of such patients would prove the influenzal nature of the meningitis. Unfortunately, however, the majority of cases of primary influenza meningitis run their course without any symptoms in the respiratory tract, without bronchitis and expectoration, thus preventing the possibility of demonstrating the influenza bacilli *intra vitam*. Lumbar puncture has not yet been tried for this purpose.

(I see from the reports of Heubner and Fürbringer† that Finkelstein anticipated me in 1895 in the demonstration of the Meningococcus intracellularis in the fluid obtained by lumbar puncture in Heubner's clinic.‡)

Influenzal meningitis can be confounded only with tubercular meningitis when the patient comes under observation with the meningitis fully developed, and, as is often the case, in hospital patients without any exact history of the nature and character of the beginning of the disease. Tubercular meningitis never begins suddenly, as is the rule in influenzal meningitis, with rigor and pyrexia, is never accompanied by herpes, and initial delirium, often present in influenza meningitis, is absent in the insidiously developing tuberculous form of meningitis.

Caution is necessary in diagnosing influenzal meningitis, as influenza, by its toxins alone or by causing hyperemic changes in the meninges, is often accompanied by violent headache, vomiting, bradycardia, and stiffness of the neck,—the latter often merely as a sequel of violent occipital neuralgia,—and may in many respects simulate the symptom-complex of meningitis. (Compare the remarks below on Pseudomeningitis.)

In considering purulent meningitis occurring in influenza we have finally still to note the variety which is observed as a sequel of croupous influenza pneumonia (Sokolowski, Kundrat, Gmeiner). Etiologically, it is to be considered on the same basis with the pneumonic meningitis occasionally occurring in genuine croupous pneumonia.

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* Compare our work upon epidemic cerebrospinal meningitis, "Centralbl. f. allg. Gesundheitspflege," 1893, xii.

† "Deutsch. med. Wochenschr.," July 2, 1896.

‡ "Charité Annalen," 1895, Bd. xx, p. 297.

The interesting reports of Krannhals on "Zur Casuistik meningitisähnlicher Krankheitsbilder" undoubtedly show that influenza may give rise to areas of hemorrhagic leptomeningitis—for so I interpret the cases described by the author—without any serous or purulent exudate in the meninges. These observations complete those described by us in which there were areas of hemorrhagic encephalitis, by showing that a similar process, probably also due to the dissemination of the germs by emboli, may also be located in the soft envelop of the brain with a relatively small affection of the cerebral cortex beneath. Here, too, the process is to be considered as nothing else than a hemorrhagic inflammation. That it is only a short step from this condition to the occurrence of a seropurulent or a purulent exudate is shown by one of our cases of hemorrhagic encephalitis, where there existed simultaneously a hemorrhagic leptomeningitis with small streaks of purulent exudate enveloping isolated pial vessels.*

Kuskow described, under the title of "hemorrhagic influenza," cases of simple hemorrhage into the meninges, especially "infiltration of blood into the pia, without a trace of an inflammatory infiltration." On the other hand, the descriptions of Trouillet and Esprit completely coincide with our combined form of disseminated hemorrhagic leptomeningitis and encephalitis, and the same is true of the communications of Cornil and those of Colin to the Paris Academy. Colin found streptococci, and therefore speaks of "meningites à streptocoques."

Under the names of "pseudomeningitis grippalis," "forme pseudoméningitique de la grippe," are embraced in the French literature (Lépine, Trastour, Lévêque, Sevestre, Guibout, Virey, Da Costa) those well-known and practically most important cases in which the disease assumes all the characters of meningitis, either from the commencement of the influenza attack or early in its course. The patients, usually children, are frequently, after an acute eclamptic incipient stage, attacked by violent headache and vomiting, soon followed by high fever, apathy, sopor, cervical rigidity, strabismus, mydriasis, inequality in the size of the pupils, and grinding of the teeth. General hyperesthesia, bradycardia, and intermittent respiration complete this picture of meningitis. The abdomen is but rarely retracted. But soon, often after a few days, this alarming condition, justifying the gravest prognosis, is replaced by the symptoms of a typical influenza. Or death may take place and pathologic findings by no means confirm the diagnosed meningitis; the condition may be merely a hyperemia of the soft envelops of the brain, or only a serous moistening of these parts ("serous meningitis").

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* Our influenza lectures, p. 30.

Kohts has described instructive cases of this sort in which children were affected. In one of these cases there was even left hemiplegia. But the expected meningitis and cerebritis were not found at the postmortem examination conducted by von Recklinghausen. "There were hyperemia of the dura mater; marked injection of the pial vessels at the convexity, as well as at the base; marked hyperemia of the gray matter of the cerebrum and the cerebral ganglia; extensive accumulation of fluid in the ventricles; no tubercles; no focal inflammation." Kohts speaks of an "irritation of the meninges without any particular reason for the same, due to the influenza micro-organisms or their ptomains."

So too in a case described by Warfvinge, which ended fatally in epileptiform convulsions, there were found at the postmortem examination only hyperemia and edema of the meninges. Regarding the cases of severe pseudomeningitis which recover within a short time, Lépine points out that these cases are probably due to a superficial recoverable or abortive meningitis. He states: "Une pneumonie ne passe pas nécessairement à l'hépatisation [solidification]; il en est qui sont presque éphémeres. De même il peut se produire des lésions de méningitide, superficielles et curables." While we completely agree with this view of Lépine, we must, on the other hand, point out that there are many cases of influenza presenting a typical picture of meningitis which recover, whose cerebral symptoms may have been due to functional toxic disturbances of the brain having no relation to meningitis.

We must finally also remember those numerous cases in which, especially in children, an otitis calls forth all the symptoms of meningitis, and in which, upon the perforation of the abscess, the alarming symptom-complex of the supposed meningitis immediately disappears.

THE COMATOSE VARIETY OF INFLUENZA.

We have previously stated that influenza occasionally commences with peculiar cerebral manifestations: with a sudden attack of giddiness and obfuscation of the senses, or with an "apoplectic"* or epileptic seizure, followed by unconsciousness lasting several hours. A patient coming out of such an alarming initial stage not infrequently recovers from what turns out to be a mild attack of influenza within a few days. We consider these to be cases of "acute intoxication by influenza toxins."

A similar pathogenesis perhaps may explain the numerous cases described in the literature in which, sometimes at the onset or sometimes during the course of influenza, there develops a marked somnolence which may lead up to coma without any other cerebral manifestations. Virey reports such cases of somnolence lasting from twelve hours to two days; Henry (Neuenburg), cases lasting eighteen hours; Barret (Hamburg), cases lasting from ten to twelve days; and Fr. Müller (Pforzheim), cases in which the coma lasted for fourteen days.

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* Compare above, p. 593; furthermore, Basqueiraz (Swiss reports, p. 153).

Cases belonging to this category have been described by Prentis, Macphail, Trastour, Ph. Wipham, Kormann, and Gibson. But even in the earliest epidemics, this comatose form of influenza caught the attention of observers.

They are mentioned by Wittich and Sennert in the epidemic of 1580 in Saxony and in Italy (Rome), by Ozanam in the year 1691, and by Beccaria (Bologna) in the year 1779. The epidemic of 1712 in Tübingen, which seems to have been distinguished by the gravest cerebral manifestations, was given the name, as reported by Camerer, of "sleeping-sickness."

In respect of similar designations in the earlier influenza epidemics —here also belongs the name cephalitis epidemica (Sauvages)—we must assume that rare and consequently striking complications gave rise to the name for the disease, for no observer of our time would think of applying such names to the more recent epidemics. It is quite possible that some so-called influenza epidemics of previous centuries were not influenza at all, but something entirely different, as, for instance, cerebrospinal meningitis.

The simple coma due to influenza toxin as one of the manifestations of the influenza process generally runs its course with high fever, a valuable point for differential diagnosis from other toxic forms, like uremic and diabetic coma. Coma as an accompanying manifestation of grave cerebral affections, like meningitis and influenzal encephalitis, obviously does not belong in this category.

Cataleptic conditions of shorter or longer duration occasionally accompany this toxic coma (Inglott, Pacini). Probably most of such cases belonged to the class of "hysteric somnolence" (sommeil hystérique), or, like N. Raw's case, to the psychoses (katatonic conditions with stupor).

This will be the proper place to consider the so-called "nona," concerning which more has been published in the lay than in the medical journals. It was supposed to be a form of influenza which appeared in May, 1890, in some parts of upper Italy, immediately after the pandemic. The patients, attacked by fever and delirium, succumbed in a few days in a state of deep coma, in some instances with pneumonia as a complication. The interpretation of nona as an epidemic of cerebrospinal meningitis (Tranjen) is not admissible on account of the occurrence of pneumonia, which is never seen in true epidemic meningitis. A pneumonia epidemic with an unusually frequent occurrence of pneumonic meningitis is a more feasible explanation, but it does not accord with the described course of the disease. Indefinite as are the reports concerning nona, its connection with influenza is, nevertheless, very probable. Perhaps it was an epidemic occurrence of the grave comatose form of influenza, as Longuet supposed, or of acute hemorrhagic encephalitis and influenzal meningitis, as Leichtenstern believed; other rare complications, as the literature shows, have been observed in a few scattered places with remarkable frequency, although, as a rule, extremely uncommon. *Adhue sub judice lis est.*

The remark of Ebstein that the lay term "nona" arose out of confusion with a medical expression, "coma," is very likely correct when we remember how the word influenza was distorted by the laity.

INFLUENZA EPILEPSY AND OTHER MANIFESTATIONS OF MOTOR IRRITATION.

We have remarked above that influenza frequently begins in children with an eclamptic seizure, and very rarely in adults with typical epileptiform attacks combined with total unconsciousness and succeeding stupor (van Deventer, Ruhemann, and others). We will now consider those cases in which, directly following the influenza attack, a typical but chronic epilepsy develops, with seizures occurring in short or long intervals. Such cases have been reported by us, by von Landgraf, Jaccoud, van Deventer in the German army reports, and in many official or collective investigation reports. So far as we know of these cases, they all, after a longer or shorter time, ended in recovery. At least we know of no recorded case in which permanent epilepsy followed influenza, although the occurrence is not thereby excluded. A case reported by us of epilepsia gravissima post-grippalis may be mentioned here.*

R. B., male, seventeen years of age, of robust stature and previously healthy, who had never had epileptic attacks, passed through a moderately severe attack of influenza without complications at the end of December, 1889. In the middle of January, 1890, he was suddenly seized with "a convulsion and unconsciousness." These typical epileptic attacks increased in frequency and intensity from day to day. Finally, 10 to 25 attacks occurred in one day. The history of the case was carefully kept from day to day. There was marked traumatic glossitis, but with the increased frequency of the epileptic seizures the whole clinical picture assumed a character different from that of ordinary epilepsy. In particular, during the intervals between the attacks, there were psychic disturbances, confusion, maniacal conditions, during which the patient indiscriminately struck about him, bit, and spoke irrationally. Then came intervals in which the patient was quite rational. Finally, the epileptic attacks increased in frequency and persisted in intensity, the maniacal periods became more acute, and we were obliged to send the patient to the State Lunatic Asylum. He made a complete recovery.

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* Our influenza lectures, p. 32.

In addition to epilepsy, many other forms of convulsions and disturbances in movement were observed during influenza or thereafter. Many of these observations recorded in literature deserve fuller mention, but we must content ourselves here simply with their enumeration.

We ourselves described* as a sequel of influenza certain peculiar clonic-tonic muscular spasms of the whole body, sometimes producing even tetanic rigidity. Tetanoid spasms of the fingers, with curious spasmic positions, occurred both in the upper and in the lower extremities. Hysteria could be absolutely excluded. Flatten has oberved a similar case. Revilliod and Determann report cases of tetany, the latter observer from Erb's clinic. Cases of pronounced tetanus, sometimes with trismus, have been observed by Revilliod, Milner, Franklin-Churchhouse. Doubtlessly the cases of tetany which occur at the acme of the influenza attack, without other grave cerebral or spinal symptoms, are to be considered as "toxic tetany," analogous to uremic tetany.

A remarkable case of tremor spasm of the left arm, combined with contracture of its muscles, is reported in detail by the German army report. We observed a case of peculiar tremor paralysis of the left arm with partial anesthesia. Recovery occurred after several months. The patient was a robust laborer in whom hysteria could certainly be excluded. Cases of "typical paralysis agitans," sometimes confined to one arm or one leg, are reported as direct sequelæ of influenza in the German collective investigation and also in reports of the Amsterdam Hospital (Bossers).

Other varieties of more persistent tremors affecting either the entire body (Hirschfeld, Wescher, Bidon) or only one extremity (Billaud) are reported in literature.

Influenza has repeatedly given rise to the occurrence of typical chorea. Such cases have been observed by Rosenstein, Leyden, van Deventer, Demme, Villard, Eichhorst, and others. Typical post-influenzal chorea we have observed in three cases in children† and once in an adult. Further there have been reported as sequelæ of influenza severe spasm of the glottis (Revilliod, P. Mejes) and spasms of the diaphragm (Kapper), and singultus of eight days' duration (Swiss reports).

Many reports in the literature regarding epileptoid tetanoid spasms, contractures, and diverse varieties of tremors may have been due to hysteria.

In alcoholic subjects influenza, like every other febrile disease, predisposes to delirium tremens. The assumption that influenza, as a rule, on account of its marked neurotoxic character, is relatively more frequently accompanied by delirium tremens than any other acute infectious disease, is quite unfounded. Certainly influenza, with its generally slight fever and its short duration, gives rise to delirium tremens less frequently than the ordinary croupous pneumonia and other acute febrile infectious diseases, such as erysipelas, septicemia, and tonsillitis. The increased frequency of delirium tremens during influenza, as reported by many hospitals, is an absolute increase due to the enormous morbidity of influenza and especially to the frequent occurrence of influenza pneumonia.

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* Influenza lectures, p. 28.

† Influenza lectures, p. 28.

The number of patients with delirium tremens admitted into the Charité Hospital in Berlin during the month of December, 1889, was double that of the previous year, and the mortality increased from 6 per cent. during 1888 to 28 per cent. at the time of the pandemic. This enormous mortality is due to the fact that among these delirium tremens patients there were numerous cases of influenza pneumonia. On the other hand, it remains a fact that delirium tremens patients attacked by influenza may, although powerful individuals in the prime of life, succumb occasionally at the height of the influenza attack and the delirium with manifestations of cyanosis and edema of the lung, while the postmortem examination shows nothing but the most intense pulmonary and cerebral hyperemia, with no gross changes in the organs, and in particular no pneumonia. Van Deventer has also called attention to such cases. The frequency of alcoholic delirium during influenza periods is noted on all sides (Rosenbach, Nagy, Bruns, and others). In the Rotterdam hospital more cases of delirium tremens were admitted during the eight-week pandemic period (1889–1890) than otherwise during a whole year (Bossers).

Hysteria and neurasthenia not infrequently arise from influenza or are enormously exaggerated by it.

All forms of hysteria have been observed after influenza, particularly hysterical convulsions and the so-called hystero-epileptic attacks, occasionally associated with fits of crying (Grasset, Krannhals, German army reports), isolated clonic-tonic spasms in the muscles of the arm, nodding of the head, spasm of the abdominal muscles, arc de cercle (van Deventer), hysteric tremor, aphonia, aphasia, various forms of anesthesia, paralyses, and contractures. We may omit quoting all names and content ourselves by calling attention to the fact that many of the cases quoted in literature as "myelitis," "cerebral monoplegia with anesthesia," and others were very probably of hysteric origin.

Post-influenzal neurasthenia generally has the characters of the hypochondriacal variety.

Is a neuropathic predisposition the basis of hysteria and neurasthenia when following influenza? This question, which we shall consider more in detail when we discuss the post-influenzal psychoses, is probably to be answered in the affirmative in most cases. On the other hand, the fact must not be overlooked that severe post-influenzal hysteria has frequently been observed in vigorous males in the prime of life, as well as in children, in whom no hereditary or acquired neuropathic tendency could be found. Worms, Josserand, Huchard, and we ourselves particularly emphasized the absence of demonstrable predisposition in these cases. "La grippe peut faire naître une hystérie, qui ne s'était jamais manifestée jusque-là." We do not wish to underestimate the significance of predisposition, but only to direct attention to the fact that the occurrence of the "hysterical" symptom-complex is occasionally less dependent upon individual disposition than upon the localization of the toxic disturbance of cerebral functions. On the other hand, in the seven cases of severe post-influenzal hysteria which van Deventer observed in children, hereditary or acquired neuropathic tendencies could be shown in each.

The influenza psychoses would naturally follow the consideration of hysteria and neurasthenia, but we prefer to discuss them at the end of this section, and first to consider the remaining previously omitted functional neuroses, taking first the affections of the spinal cord.

Cases of astasia-abasia arising chiefly on a hysteric-neurasthenic basis have been reported by Helfer, Möbius, and Herzfeld. Exophthalmic goiter as a sequel of influenza has been described by Mosler, Colley, Reinhold, Sansom, Szyszllo, and Cnyrim. Bossers reports two such cases from the Amsterdam hospital.

Certain vasomotor trophic neuroses occurring during and after influenza (general and localized redness of the skin, certain exanthematous forms, hyperidrosis universalis, symmetric asphyxia of the extremities, falling out of the hair, and premature grayness, etc.) will be considered later, when discussing the individual organs. Under the latter heading we shall also consider the importance of the influenzal and post-influenzal cardiac neuroses.

AFFECTIONS OF THE SPINAL CORD RESULTING FROM INFLUENZA.

Regarding these affections we possess numerous clinical, but only very few anatomic, reports; and there are practically no thorough and extensive microscopic observations. Below we shall give a short survey of the most important reports.

Among the earliest of these reports is the observation of Foa, who found numerous small hemorrhagic areas in the spinal cord. This disseminated hemorrhagic myelitis is analogous to our multiple focal hemorrhagic encephalitis grippalis. Under the title of "Acute Ascending, so-called Landry's Paralysis," cases are reported by Féréol, Laveran, and Arcularrus. (Compare our remarks above concerning the similar picture presented by deceptive cases of very acute polyneuritis, p. 641.) A few cases diagnosed as acute anterior poliomyelitis are described by Chilarducci, Teissier, Henoch, and Drasche. Goldflam reports two cases of "superior and inferior polioencephalitis and anterior poliomyelitis." Numerous cases of paraplegia or parapareses of the lower extremities, occasionally with paralysis of the bladder, decubitus, etc., ran their course with the appearance of acute transverse myelitis or compression myelitis. Such cases of paraplegia have been reported by Determann, Liègeois, Herzog, Gross, Fiessinger, Maillart, Lacove, Revilliod, Admiraal, and Bossers. A paraparesis of the legs with ataxia is mentioned by Leubuscher, and a case of "myelomeningitis cervicalis with softening of the cervical cord" is described by Mackay. Maillart divides five cases of grippal disease of the spinal cord observed by him as follows: (1) Cases conforming to the type of transverse myelitis; (2) cases like "myèlitide type tabes spasmodique." Such cases of "spastic spinal paralysis" of the lower extremities have also been observed by Revilliod and Herzog, who call them "disseminated myelitis." Leyden reports a case of disseminated encephalomyelitis with acute ataxia in a child, which terminated favorably. Remarkable cases simulating unilateral lesion of the spinal cord (Brown-Séquard paralysis) are described by Eulenburg and by von Determann from Erb's clinic. Peculiar transient paraplegias of the lower extremities, disappearing in from twenty-four to forty-eight hours, are described by von Vigla, and isolated paralyses of the bladder and incontinence of urine combined with "tremor of the lower extremities" have been described by Bilhaut.

The case described by us in 1890, besides many others described in literature, shows how complicated and difficult in the localization of the spinal affection caused by influenza*: A woman, forty-nine years of age, had the following symptoms immediately after influenza: Girdle pains in the trunk and violent pains in both lower extremities; a weakness of the same with marked ataxia (incoördination); swaying of the body when the eyelids were closed; pupils quite normal; total paralysis of the bladder and incontinence of urine; cystitis; no sensory disturbances; increased patellar reflexes and lively ankle-clonus. Recovery. This is a symptom-complex which cannot be classified as peripheral neuritis, tabes, spastic spinal paralysis, nor transverse myelitis. It is one of those numerous peculiar indefinable clinical pictures arising from influenza and affecting more especially the cerebrospinal system.

We cannot here further discuss the numerous fragmentary observations of post-influenzal myelitis, but we must not omit to state that many of these cases were no doubt due to neuritis or to functional, particularly hysterical, paralysis.

The remarkable influence on the nervous system exerted, as we have just seen, by the influenza process, was commented on already in earlier times (Graves, 1843; Vovart, 1880), and after our most recent epidemic especially led to extravagant pathogenetic definitions of influenza. It has been termed "central-neural-fever" (Glover) or a "vagus neurosis" which was made responsible also for the catarrhal and inflammatory manifestations of the respiratory apparatus, including the pneumonia.

A. Schmitz defines influenza as "an epidemic disease chiefly of the "nervous system," and Sell as "an infectious neurasthenia." Heidenreich in 1830 had called influenza "a disease of the ganglia with irritation of the mucous membranes." Althaus considers that all the symptoms are referable to nuclear irritation of the vasomotor centers, particularly of the pneumogastric nerve, by the influenza toxin. These hypotheses, while resting on a basis of correctly observed phenomena, miss the point because they ignore the action of the specific bacteria and their toxic products in directly causing the manifold organic lesions.

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* Our influenza lectures, p. 28.

THE INFLUENZA PSYCHOSES.

In the epidemics of past centuries the occurrence of mental disturbance as a result of influenza is recorded by various writers. But it is the last pandemic which has especially directed attention to the frequency of influenzal psychoses and to their great variety.

No other acute epidemic infectious disease—epidemic cerebrospinal fever excepted—is followed so frequently by acute and chronic psychoses, in the narrowest sense of the term. No doubt the extraordinary frequency is to a large extent an absolute one, depending upon the enormous morbidity of the disease, which in times of epidemics affects at least 50 per cent. of the population. Nevertheless, I still adhere to my former expressed opinion of the greater relative frequency of psychoses due to influenza. Even if just as many persons had been attacked by enteric fever or pneumonia as were attacked by influenza in the pandemic of 1889, not nearly so many post-typhoid and metapneumonic psychoses would have occurred as post-influenzal psychoses actually did occur. In my influenza lectures (1890) I remarked: "It has been asserted that the psychoses of influenza depended upon the "condition of nervous exhaustion ('exhaustive psychoses'); I must take exception to this view. Enteric fever lasting several weeks surely influences nutrition in general, and also the nutrition of the brain in a much more marked degree, than an influenza attack lasting but two or three days. And yet among the 2000 cases of enteric fever, and of the more than 3000 cases of pneumonia, that I have treated in the Municipal Hospital in Cologne during the last fifteen years I have not seen as many psychoses as among the 439 influenza cases in the last pandemic, even if we admit that the post-typhoid psychoses often appear late, after the patient has left the hospital, and may in this way escape the observation of the attending physician." To this we can add the experience of recent years, which shows that even up to the present time, when cases of true influenza are much rarer, we still see, from time to time, genuine post-influenzal psychoses. In explanation of the conspicuous frequency of influenza psychoses I at that time (1890) remarked that "influenza, as shown also by other observations, produces a specific nervous toxin which, besides producing the conspicuous nervous prostration, in some cases by its poisonous action on the cortex of the brain, calls forth these psychoses. The influenza toxins are powerful nervous poisons."

To these statements, which I made at that time from a small amount of clinical material, I still adhere. They have been confirmed in the observation of a largely increased number of influenza psychoses, especially in two particulars: (1) The cases observed by us were conspicuous by the fact that hereditary or other neuropathic influences were not found in them; (2) the obvious frequency with which the young, even infants, were affected by these psychoses.

In contrast to this the alienists (Ladame, Mehr, Kräpelin, Mispelbaum, Ayer, Jutrosinski, and many others) affirm, with almost complete unanimity of opinion, that the occurrence of influenza psychoses depends upon a hereditary or acquired psychopathic condition. "It would seem," says Kräpelin, "that influenza alone would not be able to produce a disturbance of the mental function in a normally constituted person." Feyr and Schüle express themselves even more definitely. According to the latter, influenza "only plays the part of an etiologic accompaniment in the production of mental disease." Ladame says: "L'influenza à elle seule ne suffit jamais à provoquer la folie."

Statements of this sort seem to us entirely wide of the mark. Without, of course, wishing to undervalue the importance of the neuropathic constitution, we must emphasize the fact that many of the influenzal psychoses observed by us occurred in entirely healthy individuals without hereditary or other stigmata.

Bossers says: "While agreeing in the main with the opinion of Kräpelin, Ladame, and others, yet I must remark that cases occur in which there was not only not the slightest trace of an inherited psychopathic disposition, but also in which, in spite of every inquiry, we could not find any grounds for assuming any acquired disposition. In these cases, I think, we are forced to the conclusion that the influenzal poison is of so toxic a nature that it alone is sufficient, by poisoning the cortex of the brain, to develop a psychosis. It was not possible in my two cases to find the slightest predisposition. Althaus, Mucha, Ulliel, also admit the possibility of the occurrence of an influenza psychosis due to influenza alone, without any nervous predisposition."

Gray reported, in the epidemic of 1782: "Symptoms of mania were sometimes produced by it, where no predisposition to that complaint could be traced."

Kirn, in 22 "febrile psychoses," that is, in those which commenced during the febrile stage of influenza, could find a hereditary or acquired disposition only five times, that is, in 23 per cent.; but, on the other hand, 47 times in 51 postfebrile psychoses, that is, in 92 per cent.

It seems to me that the etiologic conception of "hereditary tendency" is extended beyond reasonable limits; for instance, when traced back to grandparents and great-grandparents. The same is true of the conception "acquired disposition." Thus in the above-mentioned 92 per cent. of predisposed influenza psychoses, the "acquired disposition" is referred to "injuries to the head occurring in youth or a hysteria and neurasthenia or to later chronic affections of the most varied kinds (stomach, lung, heart, and head affections). With so comprehensive an "acquired disposition," 92 per cent. of predisposed cases can readily be gotten together.

The contradiction between my own experience and that of the alienists I can explain only on the supposition that the prolonged chronic psychoses, on account of which the patients were finally handed over to lunatic asylums, occurred mostly in neuropathic individuals, especially in those with a hereditary taint.

A number of these post-influenzal psychoses we kept in hospitals until convalescent, usually after one or more weeks. Of others whom we handed over to the lunatic asylums on account of suicidal tendency or disturbance we heard later that they were soon discharged from these institutions cured. We then regretted that we had not kept back such patients, for the placing of a patient in an insane asylum is not a matter of indifference and should be avoided if possible.

As regards the time of occurrence of influenza psychoses and the different forms of mania, we cannot, of course, examine in detail the copious special literature on this subject.

In very rare cases there may be a prodromal stage, lasting one or more days, of acute afebrile or subfebrile dementia, preceding the influenza attack, it being principally of a melancholic type, with fear, stupor, occasionally also with paranoia, exaltation, increasing to acute mania. Such delirium or dementia is quite analogous to that which occasionally ushers in typhoid fever or pneumonia. (Compare p. 594.) It is quite characteristic of these prodromal psychoses that with the onset of fever and the beginning of the true influenza attack, quietude and consciousness are restored. By the end of the influenza attack the patient has quite recovered, and, furthermore, it is peculiar that this prodromal afebrile delirium and initial psychosis protect from dementia during convalescence rather than predispose to it. No doubt this is due to a purely transitory toxic influence and there can be no question of a peculiar "hereditary or acquired" disposition in these cases. The conditions just described have naturally nothing in common with an initial delirium tremens.

The psychic disturbances occurring during the febrile stage of influenza fall into the class of febrile deliriums, which are nothing but acute transitory toxic mental disturbances. They generally run a uniform course, with more or less total disturbance of consciousness, confusion, with either quiet or excited delusions and hallucinations. They may also simulate many forms of psychoses in a more "limited sense of the term": either the melancholic type, with stupor, fear, total dumbness, refusal of food, and ideas of persecution; or the maniacal type, with fleeting ideas, psychic exaltation, and motor disquietude up to mania; or, finally, the type of hallucinatory confusion. As in all febrile psychoses, there is in influenza also not rarely a marked disproportion between the intensity of delirium and the height of the fever. It is characteristic of the simple, febrile delirium that it ceases with the falling of the body temperature—that is, after the influenza process has ceased.

Psychoses, in the limited sense of the term, occasionally develop, but very rarely, out of the febrile delirium, and are then characterized by the above-noted various psychic disturbances continuing for a shorter or longer time beyond the febrile period.

In the majority of cases the commencement of a psychosis follows immediately after the termination of the influenza attack, or in some instances a few days thereafter; less frequently after an interval of one or two weeks. In the latter case it is difficult to conceive the toxic influence still at work. Very likely these conditions are due to after-effects, to disturbances in the nutrition of the cerebral cortex induced by the toxins, and progress during convalescence being favored in their course by the other evil after-effects of influenza. The general bodily and mental prostration, the insomnia, the anorexia, and the digestive disturbances, sometimes with the addition of excruciating neuralgia, prepare the soil for intense mental depression and hypochondriacal melancholia, which may increase to grave melancholia with an apathy for existence and suicidal tendencies,* with maniacal ideas and delusions of poisoning and persecution, hallucinations, etc.

Undoubtedly the condition of depression, the hypochondriacal melancholia, and the severer forms of melancholia are the most frequent of the post-influenzal psychoses. But very nearly all other varieties of acute mental disease are observed after influenza, especially hallucinatory confusion with considerable disturbance of consciousness, with delusions and insane ideas, principally of a depressive, rarely of an exalted, character, with either absence or presence of motor disturbance, which may occasionally also be increased. These are the so-called "exhaustion or collapse psychoses" of alienists.

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* During the time of the pandemic of 1889–1890 the number of suicides in Paris increased 25 per cent. (quoted from Bossers).

A third, by far rarer, form of post-influenzal psychosis is the maniacal disturbance characterized by fleeting ideas and chattering incoherence, with varying but usually exalted moods, great restlessness, which may increase to destructive or maniacal fury. Conditions of this nature are sometimes difficult to differentiate from the excited form of the "hallucinatory delusions." The German collective investigations record four cases of mania in children.

We will omit describing yet other forms of post-influenzal psychoses which are classified under the title Acute Paranoia and Dementia Acuta. The first signs of "general paralysis" have often followed influenza (Althaus).

It is obvious that in numerous patients in whom there was latent mental affection or who were on the borderland influenza caused its final resolution. Since all these patients, in whom, of course, the idiopathic psychosis was merely precipitated by influenza, came into lunatic asylums, the assertion of the alienists that only those who were predisposed became mentally deranged by influenza is not very surprising. Kirn has proposed for those cases the term "pseudo-influenza psychosis"; by Bidon they were more accurately termed "idiopathic psychoses becoming evident as the result of the influenza attack."

The post-influenzal psychosis, like the initial or prodromal psychosis, is frequently of only short duration. In severe cases it may last for weeks and months. The prognosis, as a rule, is very favorable, corresponding to the acute toxic character of these psychoses. Probably but very few individuals, possessed of a hereditary or neuropathic taint, suffered from permanent mental disturbance after influenza. But many merely became insane rather earlier than they would have done without influenza.

SYMPTOMS REFERABLE TO THE DIGESTIVE APPARATUS (INCLUDING PERITONEUM, SPLEEN, AND PAROTID GLAND).

In most cases of influenza the symptoms arising in the digestive apparatus are but slight and limited to transitory anorexia during the febrile stage. But gastro-intestinal forms occasionally occur, and in them the symptoms due to the gastro-intestinal tract predominate, chest symptoms are absent, and the nervous symptoms, such as the headache, do not amount to more than the general "cephalæa gastrica." In these cases the tongue, which in influenza is usually moist and only slightly coated, is thickly coated with a dirty white layer; vomiting—frequently an initial symptom—becomes constant, and may be of a bilious character. The breath is offensive; the appetite is entirely lost; the epigastrium is tender to pressure (the frequently noted "influenzal hyperesthesia of the stomach"). Cardialgia may be present. Instead of the usual constipation, there is diarrhea, with abdominal pain, and often distention of the abdomen. Some French authors assert that these purely gastro-intestinal forms are characterized by but slight fever and an especially protracted course.

In simple uncomplicated influenza the tongue is never dry or "typhoid"; almost invariably it is moist and broad. As a rule, it is but slightly coated, and is often bright red at the tip and edges.

Under the name "characteristic influenza tongue" J. Terry and others have described very various conditions. There is nothing characteristic about the tongue in influenza, as in enteric fever or scarlatina. A uniform intense reddening of the entire tongue, called glossitis, is noted by several observers. The most detailed description is given by Bristowe, who even gives statistics in regard to it. He found the tongue "normal" in 11 per cent.; "pale and flabby" in 44 per cent.; "furred" in 41 per cent.; "red and dry" in 4 per cent., of his cases.

The mucous membrane of the mouth is often reddened; that of the palate and of the pharynx, occasionally in patches, as has been noted by Warn, Linden, Forssberg, and ourselves. Some of the older authors (Tigri, Haesser) have also noted the condition. Cases of *stomatitis simplex*, *vesiculosa*, and even *ulcerosa* have also been described.

Reddening and swelling of the tonsils, including the pharynx, have been frequently observed. Lacunar, phlegmonous, croupous, or diphtheric tonsillitis is always due to a mixed infection.

"Tonsillitis" or "angina erythematosa" was found by Stintzing in 60 per cent.; by Anton, in 29 per cent.; by Schulz, in 30 per cent.; by Kirn, in 33 per cent.; and by Preston, Bristowe, and the Bavarian army report, in 3 per cent. of the cases.

Löwenstein describes a "hemorrhagic angina." Hemorrhages from the gums, root of the tongue, and pharynx are often mentioned in the literature. (Compare pp. 602 and 603 upon this point.)

Vomiting has very generally and correctly been described as a frequent initial symptom of influenza. Anton observed it in 21 per cent., and Stintzing in 25 per cent., of their cases.

The bowels may be regular or costive; diarrhea is less common; Stintzing found the latter in 25 per cent.; Schulz, in 20 per cent.; Krehl, in 13 per cent.; Anton, in 8 per cent., of their cases. The most detailed account is by Bristowe. He found the bowels normal in 72 per cent., constipation in 11 per cent., and diarrhea in 12 per cent., of his cases.

If in any case the phenomena of a severe intestinal influenza (diarrhea, meteorism) are combined with those of the nervous form (headache, delirium, apathy), and more especially if there is also high protracted fever, we get the much-quoted "typhoid form of influenza." The clinical picture becomes yet more deceptive if, at the same time, the tongue is dry or roseola appears; Teissier often observed this latter. Curschmann, in the Leipsic clinic, found it in 1.2 per cent. of all the cases of influenza. But we have called attention above to the fact that there is but rarely any serious difficulty in the differential diagnosis between typhoid influenza and enteric fever. Often a single symptom will suffice to clinch the diagnosis of influenza, for example, the sudden onset with rigors and immediate high fever, or the occurrence of herpes labialis, or the intense initial head, back, and joint pains, or the appearance of *hyperidrosis universalis*. There is frequently a resemblance to enteric fever, but the tongue is then quickly covered, as if by cement, a symptom of the gastric variety of influenza only, and the diarrhea is different to that of typhus abdominalis, etc.

There is no doubt that, as in all the complications of influenza, the typhoid forms occurred with special frequency in certain places (Wörner, Teissier, Trechsel).

Very remarkable is that form of influenza—it might be called the metamorphous variety—which is at first entirely gastro-intestinal, and then in a few days suddenly changes into the respiratory variety, with diffuse bronchitis and pneumonia. At the same time the gastro-intestinal phenomena fall into the background. The sudden change of the clinical picture in these cases often is very surprising.

One addition to the pathology of influenza furnished by the most recent epidemic is the demonstration that influenza may give rise to acute hemorrhagic gastritis and enteritis, and sometimes, as a sequel, also to peritonitis.

Many cases of simple intestinal hemorrhages, as well as of severe bloody, mucous, dysenteroid diarrhea, in influenza, have been described (Landgraf, Enggesser, Fürbringer, B. Auerbach, Warfvinge, Melin, Lennmalm, German army report, official report from Bavaria, from Switzerland, etc.). The intense hyperemia of the intestinal mucous membrane frequently found upon postmortem examination, with the addition of ecchymosis and streaky hemorrhages, is sufficient to account for the simple intestinal hemorrhage. This variety of hemorrhage from the intestine is analogous to epistaxis and to the influenzal hemorrhages of the pharynx, larynx, and bronchi.

This hyperemia of the intestinal mucous membrane may progress to inflammation, necrosis, and ulceration. We quote Jürgens, who in postmortem examination of many cases of influenza found "severe ulcerative or hemorrhagic pathologic conditions of the gastric and intestinal mucous membrane. In the stomach broad, often long, but not deep ulcerations of the gastric and intestinal mucous membrane, which, besides being markedly hemorrhagic and hyperemic, were intensely swollen and edematous. The submucosa and, to a certain extent, the muscularis also, were edematous and the seat of cellular infiltration, as in commencing phlegmonous gastritis. With marked hemorrhagic enteritis there was also considerable swelling of Peyer's patches."

Klebs and Lubarsch found ulcerations of Peyer's patches which, for a moment, gave rise to a suspicion of typhoid. Flesch found ulceration of the jejunum and swelling of the mesenteric glands. Kuskow has made the most detailed study of these conditions, especially the "hyperemic" inflammation and the resulting necrosis of the mucous membrane, more particularly of Peyer's patches and the solitary follicles. These conditions were most frequently found in the duodenum; then in the stomach, ileum, and jejunum. Mosler describes a case of "gastro-enteritis hæmorrhagica" of considerable clinical interest. Weichselbaum described cases of hemorrhagic enteritis of the small intestine and of croupous enteritis. In two such cases he found the Diplococcus pneumoniæ in the intestine.

We may briefly describe a case of Weichselbaum's: A girl, twenty-one years of age. Influenza. Epileptiform convulsions; vomiting; diarrhea; herpes nasalis. Slight distention of the stomach, and especially of the right iliac region. Death on the eleventh day. Post-mortem examination: Bronchopneumonic areas. Acute enteritis of the ileum. Bloody contents in the small intestine. Mucous membrane swollen, partly much injected, and partly the seat of hemorrhagic infiltration.

The grave form of influenza enteritis may, in consequence of the circulatory disturbances in the intestinal walls, give rise to paresis of the gut with meteorism and persistent constipation, and even to obstruction (see below). The intense abdominal pain, the frequent vomiting, and the collapse may simulate the features of general peritonitis.

If the influenza enteritis attacks only the lowest portion of the ileum and the cecum, with marked pain in the region of the appendix, the picture of appendicitis may be produced. "Nous l'avons vu simuler une pérityphlite classique" (Teissier).

The cases termed "typhlitis and perityphlitis following influenza," which occur in the reports from all countries, are to be thus explained, except that they were not usually, as assumed, cases of appendicitis, but of a true typhlitis.

In the pandemic of 1889 I observed some cases of simultaneous influenza with typhlitis which I did not venture to bring into direct causal relation with the influenza; I believed that I had to deal with a coincident occurrence of influenza with an ordinary appendicitis. But the subsequent accumulation of reports in the literature, together with my own pathologic experiences (see below), have since convinced me of the existence of an influenza typhlitis.

We have frequently laid stress on the fact that the rarest complications of influenza occasionally occur in local groups: this applies also to typhlitis. Teuscher (Saanen) saw, within three to four weeks, 12 influenza patients with typhlitis.

The severe form of influenza enteritis may lead to peritonitis, generally with a fibrinous, rarely with a purulent, effusion. The following observations of our own may serve as instances:

1. A boy, aged twelve, was suddenly taken ill with convulsions, high fever, and all the signs of the respiratory form of influenza. At the end of the second day violent abdominal pains; retraction of the abdomen; extreme sensitiveness to touching the abdomen, particularly in the region of the cecum; vomiting; constipation; collapse. In the following days meteorism with diarrhea set in. Death on the sixth day. Postmortem examination: The peritoneal surface of the lowest portion of the small intestine and the cecum was of a dirty-red color. Fibrinous deposits on the inflamed coils of intestine. No fluid exudate in the peritoneal cavity. The mucous membrane of the lower portion of the small intestine, of the cecum, and of the ascending colon was of a dark-red color, and in the condition of the above-described hemorrhagic enteritis. Appendix intact.

2. Typical beginning of influenza (in the pandemic of 1889) in a woman forty-five years of age, with rigor and high fever. On the third day, symptoms of peritonitis; meteorism; vomiting. At first two bloody diarrheic stools, then total constipation.

On the eighth day, with continuance of the fever, total obstruction with fecal vomiting. In the left iliac region a large intestinal coil projects and is easily defined. A surgeon called in consultation recognizes von Wahl's sign, and in spite of the high fever pronounces it to be a volvulus of the sigmoid flexure. The operation is fixed for the next morning. The patient died during the night. Postmortem examination: The intestines are normal as regards position. Peritoneum of a dark-red color; slight fibrinous peritonitis. The mucous membrane of the lower portion of the ileum is of a dark-red color and swollen. The mucous membrane of the ascending colon and the sigmoid flexure, which latter seems much distended and thickened, is of a dark-red color, and in the condition of the above-described "hemorrhagic diphtheric enteritis."

Peritonitis as a sequel of influenza is repeatedly mentioned in the official German collective investigations. Such cases have also been described by Kundrat, Kelsch and Antony, Wallis, Buchheim, Sirotinin, Isnardi, Cnyrim, and in the Swiss reports. Kuskow describes a case of local peritonitis in the splenic region which originated from a "parenchymatous necrosis" of the spleen. "Influenza peritonitis," so far as at present known, exists only as a sequel of the severe form of influenza enteritis described above. There is no convincing instance recorded to show that the influenza bacilli can pass directly into the peritoneum from the blood or from the intestine with mucous membrane intact, and there cause peritonitis, even granting, however, that such a case as that described in the German army report deserves consideration. The presence of the influenza bacillus in the intestine in hemorrhagic enteritis or in the peritoneum in peritonitis has not yet been established.

The gastro-intestinal influenza may give rise to a severe vomiting.

Böse* (Cologne) observed in an influenza pneumonia a "gastroenteritis acutissima" which had the appearance of a severe attack of cholera, but it terminated favorably.

Holz saw two children who, on the second day of influenza, were attacked by a "cholera-like enteritis with convulsions and unconsciousness." After a coma of twenty-four hours they awoke and recovered without interruption. Simon points out that influenzal gastro-enteritis occasionally sets in with very alarming symptoms of acute collapse, but, nevertheless, ends in remarkably rapid recovery. Such cases, which resemble cholera or an acute alimentary toxemia, are mentioned by Warfvinge, and particularly in the official reports from Bavaria, Baden, Hessen, etc. Harder and Behier called attention already in 1830 in Paris to the similarity of intestinal forms of influenza to cholera.

The gastric and other digestive disturbances continue occasionally long into convalescence, and thereby give rise to severe nutritive disturbances and frequently to marked loss of weight.

Besides a case of *hyperemesis incoërcibilis* as a sequel of influenza, in a man nineteen years of age, who was anything but hysteric,† we observed many cases in which complete anorexia and other gastric disturbances continued for weeks after convalescence from influenza. The affected patients became markedly emaciated. In older individuals this produced a chronic "influenza cachexia" which often suggested a more serious gastric affection (carcinoma) until this apprehension was removed by recovery, often much delayed.

An exceedingly robust and stout brewer, forty years of age, during the seven weeks following influenza, by reason of complete anorexia, decreased in weight from 105 to 72 kilos. His appearance was so altered that his friends did not recognize him.‡

Elste (German marine report) found loss of body weight in all cases. It was occasionally very marked, even up to 11 kilos, in cases of but five days' duration; the average was 5 kilos. The health report from the Grand Duchy of Oldenburg contains the following: "Some persons showed, within fourteen days, a decrease of body weight up to 7.5 kilos." Pribram, who weighed daily the patients in his own family, found, even in the first few days, marked loss in weight. Brakenridge (Edinburgh) and Umpfenbach report the same fact.

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* Our influenza lectures, p. 36.

† *Ibid.*, p. 33. An analogous case mentioned by Revilliod. ‡ *Ibid.*, p. 33.

Liver.—As regards influenzal hepatic disease, the reports are mainly pathologic. Hyperemic conditions, parenchymatous degeneration, cloudy swelling, small-celled infiltration, microscopic tissue necrosis, and formation of thrombus (Kuskow) are mentioned.

The conditions for the formation of abscess of the liver, of which Krannhals and Cimbali have observed a case, are present in the severe forms of hemorrhagic-ulcerative enteritis. The statements concerning acute yellow atrophy of the liver after influenza are to be received with extreme skepticism. Reynal describes a case of "icterus gravis" after influenza.

Experiences concerning the frequency of icterus in influenza are very varied. It is mentioned by Lancisi (1709) and by Huxham (1737) as an occasional occurrence,—"some fell into jaundice,"—as well as by many later authors (Stoll, 1775, and others).

Peacock, in his description of the epidemic of 1847–1848, remarked that "a frequent symptom was a feeling of heaviness and pain in the right hypochondrium, which was generally combined with a certain amount of icteric discoloration of the conjunctivæ or the skin in general." Bäumler observed, in the last pandemic, "icterus, or at least icteric discoloration, of the sclera," in 88.5 per cent. in males and in 76.8 per cent. in females—that is, practically always. He considers, therefore, that jaundice is an "important diagnostic symptom" and "an important prognostic sign." Bile-pigment was not, but urobilin was, found in the urine. He thinks the jaundice probably hematogenous, caused by the destruction of red blood-cells.

In our 439 cases in the pandemic of 1889–1890 we recognized the presence of jaundice only twice during convalescence from influenza, but we must admit that we did not look for traces of icterus in the conjunctivæ. We did so with great care in the following epidemic, but with absolutely negative results. But it is possible that our standard of "weakly icteroid," "subicteroid," color of the sclerotic differs from that of other observers. The hospital statistics of Hamburg, Leipsic, Munich, Würzburg, and the English authors and statisticians (Preston, Bristowe, Parsons) do not mention jaundice at all.

In the German collective investigations only 2 per cent. of the reporters mention jaundice, and in the collective investigation of Breslau, of 234 physicians who sent returns, only four of them reported cases of jaundice. Gutmann (Nuremberg) and Senator mention that they observed jaundice twice. Comby saw icterus but once among 218 children, while Weiss (Neumarkt a. R.) observed it four times in 110 cases. On the other hand, Rota (Bamberg) and Bergmann (Pottenstein) saw "numerous cases of icteroid discoloration of the conjunctivæ and skin, as well as marked catarrhal jaundice," and the medical officer for the district of Merseburg reports, as the result of information supplied by the physicians of his district, that "in all the febrile cases, whatever the form of the disease, there was slight jaundice of the skin and eyes, as well as bile-pigment in the urine."

There can be no doubt that jaundice occurs but very rarely in influenza, provided we do not count as such every suspicious yellowish discoloration of the posterior fatty layer of the scleral conjunctiva. But since all, even the rarest, complications of influenza occasionally accumulate in particular localities, this may have been the case with the concomitant jaundice in Freiburg, Bamberg, Pottenstein, and Merseburg. These exceptions are very remarkable; possibly in these cases there is a mixed infection with the, still hypothetic, etiologic cause of the so-called "catarrhal icterus." But it is impossible to consider jaundice in influenza as of "general pathognomonic-diagnostic significance."

Spleen.—In influenza, as a rule, the spleen is but rarely so much increased in size that a distinct enlargement can be demonstrated at the bedside. This applies particularly to the immense majority of mild cases. But in several cases (about 15 to 20 per cent.) influenza, simple as well as complicated, gives rise to definite splenic enlargement, which can be determined with certainty during life, and whose existence is frequently confirmed at the postmortem examination.

But the statements regarding the condition of the spleen in influenza are remarkably contradictory.

While the pathologists, Birch-Hirschfeld "generally found no changes in the spleen," and Jürgens "had seen no splenic tumor," Ribbert, on the other hand, found "the spleen occasionally enlarged to several times its ordinary volume, and in all (8) some enlargement." In agreement with this author and other pathologists (Wallis) we too occasionally observed marked increase in the size of the spleen in a number of postmortem examinations; so, too, Drasche found "in all influenza cadavers acute and sometimes considerable enlargement of the spleen," while Winogradow found it only twice in 13 autopsies.

Kuskow has studied the pathologic condition of the spleen in influenza most thoroughly. He found it enlarged 12 times among 40 autopsies, generally but slightly; in the remaining 28 cases the spleen was smaller and "often considerably lessened in size." The following are the principal characteristics of the "typical influenza spleen": The capsule is shriveled, the pulp is gray or dirty-violet, of the consistence of a rotten plum, and studded with dark-red areas. Microscopically there is swelling of the endothelium of the veins and arteries, so that the lumen of the small arteries is often entirely obliterated. In other places one finds thrombi in the veins and capillaries. Together with these changes one finds blood extravasations and tissue necrosis of both the trabeculæ and of the pulp. Only rarely are micro-organisms met with and then only in small numbers.

Very different and even diametrically opposed are the statements of clinicians regarding the size of the spleen in influenza. Strümpell, Fleischer, Rosenbach, Runeberg, Regnier and Comby, Swajser and Dunin, Begejawlensky could never find splenic enlargement; Peiper could find it but twice among 217 cases; Vesterdahl but once among 73 patients; and Holmberg and Linden but twice. Very small percentages are recorded by Meckel (Nuremberg) and Höfler (Tölz), namely, 2 per cent.; H. Rieder (Munich), 3 per cent.; Stintzing and A. Fränkel, 5 per cent.; and Golowin (St. Petersburg), 8 per cent. The condition of the spleen attracted the attention of English observers but little. The statistics of Bristowe, Preston, Robertson, and Elkins, to which such frequent allusion has already been made, contain no mention of the spleen in influenza. All that I could find can be embraced in the sentence: "Enlargement of the spleen in a small and uncertain proportion of the cases" (Thompson).

In marked contrast to these statements are numerous others, according to which the influenzal splenomegaly is of very frequent occurrence.

Sokolow and Kernig describe enlargement of the spleen as a constant feature. It was observed in the city hospital at Dresden in 80 per cent. of the cases; in Hamburg, in 56 per cent.; by Bäumler (Freiburg), in 63.5 per cent.; and by Schnaubert (Petersburg), in 39 per cent. Goll (Zürich) describes it as of very frequent occurrence. An intermediate position is taken by the following authors. Enlargement of the spleen was found by Guggenheim (Würzburg) in 25 per cent. of cases; by Anton (Würzburg), in 16 per cent.; and by Aufrecht, in about 20 per cent. We found it in 14 per cent., and Gutmann (Nuremberg), in 11 per cent.; Krehl and Fischel each in 10 per cent.

In the French reports the frequency of enlargement of the spleen is almost invariably mentioned by Potain, Chantemesse, Guyot, G. Sée, and Mangoubi.*

The diametrically opposed statements concerning the spleen can by no means be excused by the fact that the cardinal question, "How many centimeters must the spleen measure to be considered enlarged?" cannot be answered with exactness, for the normal size of the spleen varies. A volumetrically normal or even enlarged spleen, if spheric, may appear small upon percussion, while a very flat, disk-like spleen, of normal size, may, under the same circumstances, appear enlarged. The pathologist is in a better position to judge by the total volume of the spleen, and may thus recognize that a volumetrically normal sized spleen is "swollen" by other criteria (stretching of the capsule, turgescence of the organ). But the clinician must be careful not to attempt too minute deductions from the percussion area of the spleen as measured in centimeters.

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* "Splènomégalie grippale," "Thèse de Paris," 1895.

Attempts have been made to explain the contradictions just mentioned regarding the spleen in influenza. Kuskow believes that the variance in views is due to the different virulence of influenza in different places. Others believe that the accumulation of complicated cases, especially those with pneumonia, has given rise to the aggregation of cases with enlargement of the spleen. Another explanation often put forward is that enlargement of the spleen occurs frequently in the gastro-intestinal form, and when this form prevailed, there too splenomegaly was often found. But all these attempts at explanation are inadequate and do not go to the root of the matter. As a matter of fact, these extremely contradictory views are the result of nothing else than the attribution of an exaggerated value to percussion, and the consequent assumption of an increase in the size of the spleen from percussion, when more cautious observers would hesitate to draw this conclusion. On the other hand, some modern observers go too far in depreciating the value of percussion of the spleen when they lay so little stress on the result of this excellent method of examination as to consider only a palpable spleen as enlarged.*

Bäumler, in 122 cases of splenic enlargement, found the spleen palpable in 23 cases, and in the remaining 99 cases the enlargement was demonstrable only by percussion.

We found the spleen enlarged in 62 cases. Among these the organ was plainly palpable in 49 cases; and in 13 cases the enlargement could be demonstrated only by percussion.

The relations of the palpable spleens to those found enlarged only by percussion were as follows:

By Bäumler...........	19.0 per cent. palpable;	81.0 per cent. enlargement on percussion.
By us..................	79.0 " " "	21.0 per cent. enlargement on percussion.
By Anton (Würzburg)..	87.5 " " "	12.5 per cent. enlargement on percussion.

These figures explain, without any further comment, why one observer could find it in 63 per cent., and the others only in 14 and 16 per cent., of enlargement of the spleen.

The contradictory experiences of the pathologists are easily explained. The pathologic material was provided principally by those who had survived the true influenza attack and who had subsequently died from complications or sequelæ, and considering also the slight mortality of influenza, the pathologic material for observation was everywhere very meager. When such conditions exist, the results are very irregular.

Unexplained, however, is the fact that numerous clinical observers never found an enlargement of the spleen in spite of the large number of cases which came under their observation.

Parotitis, an occasional complication of all infectious diseases, also occurs occasionally in influenza. It was recorded, so far back as the epidemics of 1580, 1732–1733, and all the following ones, occasionally in conjunction with orchitis (compare p. 684) or with erysipelas of the face. In these cases there is undoubtedly "mixed infection." In all collective investigations of the most recent pandemic, parotitis is mentioned as a rare complication. Of the 55,263 patients in the German army, 12 showed this complication; of the 3185 reporters of the German investigation, 37 mentioned parotitis. Fiessinger and we ourselves early called attention to this complication.

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* Compare our influenza lectures, p. 34.

SYMPTOMS REFERABLE TO THE CIRCULATORY APPARATUS, INCLUDING BLOOD, THYROID, AND LYMPH-GLANDS.

Influenza affects the heart in various ways. The influenza toxins may harm the heart muscle directly; generally, however, the toxic influence is limited to the cardiac nervous apparatus. Indirect influence is exerted upon the heart by the elevation of temperature, but more particularly by the affection of pulmonary circulation characteristic of influenza, viz., hyperemia of the lungs, capillary bronchitis, and pneumonia, processes which, in turn, acting partly mechanically by disturbance of the circulation and partly chemically by the increase of carbon dioxid in the blood, influence the heart and consequently the whole circulation.

We will not here enter into any exhaustive discussion in what manner influenza and its pulmonary complications influence the heart, the circulation, and the composition of the blood. We will confine ourselves to a few important points.

The pulse-rate corresponds, as a rule, to the height of the fever, but the degree of tachycardia is usually proportionately higher than the rise of temperature, a point which, in agreement with Drasche, Vesterdahl, Sansom, and Bahrdt, I emphasized some time ago in opposition to some other observers. Especially in those cases of diffuse bronchitis and bronchiolitis with dyspnea and cyanosis there is regularly a very marked tachycardia, notwithstanding an afebrile or subfebrile course of the disease. Frequently the pulse shows a marked cardiac weakness, quite disproportionate to the slight fever which is revealed on the sphygmogram (Pribram, our lectures) by a marked dicrotism.

Bradycardia occurs in influenza more often than in any other acute infectious disease. Here again the neurotoxic character of influenza is manifested, for we cannot assign any other cause for this remarkable, often perfebrile, bradycardia, or for the afebrile tachycardia in simple uncomplicated influenza, than the influence of the toxin on the vagus or other centers which regulate the cardiac beat.

Influenzal bradycardia was mentioned by Rutty (1762), by Hodson (1800), in the recent pandemic by Stintzing, Strümpell, Hefforn, Barthélémy, Ruhemann, Ward, Farbstein, and by ourselves. In the garrison hospital of Munich, among 275 patients, 46 per cent. of them were found to have "a marked slowing of the pulse, frequently combined with irregularity, and lasting from ten to twelve days."*

Bradycardia may be either absolute (a pulse of 48 to 60 with an afebrile or subfebrile course) or relative (pulse of 80 to 120, with high fever—from 39° to 41° C.). It even occurs in severe influenza pneumonia, as Rankin and ourselves pointed out.

In one such case observed by us, which occurred in an individual twenty-seven years old with influenza pneumonia, we found the following numeric relations between temperature and pulse-rate: 40.7°: 106; 39.8°: 96; 40.1°: 92; 39.8°: 88; 39.3°: 94, etc.

Rutty (1762) well described this phenomenon: "But in general the pulse is not quick, and even when the feverish symptoms were very high, it was often observed to be not more quick than in health."

Huchard describes as a characteristic manifestation due to "disturbed cardiac innervation" (vagus weakness) the "pouls instable," in which condition the pulse-rate is rapidly increased by an alteration of posture from the recumbent to the erect—an increase such as from 80 to 120 beats. This is an old, well-known phenomenon occurring especially in convalescence from febrile diseases and in "weakened hearts."

There is another occasional anomaly of influenza which requires repeated careful counting of the pulse for its detection; it is very frequently present also in epidemic cerebrospinal meningitis. This is the allorrhythmia or poikilorhythmia, in which the pulse-rate is variable, constantly changing within narrow limits, so that, for instance, in eight successive quarter minutes the following numbers was counted: 25, 24, 28, 28, 26, 25, 28, 26. Heubner also emphasizes the "marked variations in pulse-rate" in influenza.

Allorrhythmia forms a transition to the graver forms of arhythmia, generally combined with tachycardia and seen sometimes in uncomplicated influenza, even in young individuals.†

Angina pectoris or stenocardia was observed by several authors (Röhring, Pawinski, Ruhemann, Teissier, Sansom, Huchard, Duflocq), sometimes as a transitory phenomenon during the influenza attack, but more frequently as a persistent sequela, and often in strong individuals with sound hearts and in the prime of life.

In rare cases, even in uncomplicated influenza, alarming symptoms of cardiac weakness with attacks of syncope may occur in individuals who have previously had no heart trouble, either at the acme or at the end of the attack (Teissier, Drasche). Cases of sudden death due to "cardiac paralysis" occurred most frequently during the period of convalescence. They are mentioned in the epidemics of 1729, 1732, and 1755, and recently by Pribram, Drasche, Back, and Braubach, in the reports of the Swiss Board of Health and by ourselves.

* German army report, p. 59.

† Influenza lectures, p. 32.

Drasche says: "Influenza has often a veritably toxic influence on the hearts of otherwise healthy individuals. Occasional irregularity of the pulse, accompanied by remarkable frequency and smallness, is often the first sign of the malignant character of the disease, which not infrequently causes sudden death by cardiac paralysis."

To our own impressions of the effects of the pandemic we gave expression at the end of the epidemic as follows: "That influenza is frequently followed by serious, long-continuing, and persistent functional disturbance of the heart of a neuropathic or myopathic origin is taught by a series of recent observations; we frequently saw vigorous people in the prime of life who, some weeks after recovery from an attack of influenza, complained of shortness of breath, attacks of angina pectoris, palpitation of the heart, and inconveniences, in whom, beyond an occasional marked tachycardia or arhythmocardia with smallness of the pulse, no other signs of cardiac affection could be found. In Cologne, after the pandemic, some notable cases of sudden cardiac failure occurred in persons who, convalescent from a more or less severe influenza, had again taken up their vocations. I think it not unlikely that this was due to the influenza from which they had just recovered."

The danger to the heart is all the greater if previous pathologic changes of this organ exist, such as weak heart, fatty heart, valvular defects, or arteriosclerosis. We repeatedly saw, as also did Drasche, cases with stationary, fully compensated valvular lesions occasionally suffer, as a result of influenza, from a transitory or sometimes a permanent injury to the heart, which some weeks or months later caused death, due to cardiac incompetence, with or without recurrence of the endocarditis. Kahler repeatedly saw death follow in patients with heart disease "within a short space of time, always with the signs of acute purulent bronchitis." On the other hand, as Krehl, Warfvinge, and we have remarked, many individuals with cardiac disease passed through an uncomplicated attack of influenza with the same ease as healthy individuals.

Pignoll and Teissier described cases of "acute dilatation of the heart," particularly of the left ventricle, following directly on influenza.

Some processes, as well as the previously mentioned severe attacks of cardiac weakness and acute cardiac failure, point undoubtedly to changes in the heart muscle. Yet Peter, Pawinski, Stiller, Teissier, and particularly Huchard consider the influence of the influenza toxin on the nervous mechanism of the heart to be the chief factor; they, therefore, speak of a "fatal disturbance of the cardiac innervation," of a "nervous cardiac death," or of "death due to vagus paralysis." Although these hypotheses go perhaps too far, there can be no doubt of the nervous origin of the numerous and often severe affections of the heart in influenza.

In support of this view the following considerations may be added: The transitory character of many of the cardiac disturbances and their acute occurrence—*e. g.*, the stenocardia, the arhythmia in young individuals with previously quite healthy hearts, and in subfebrile or mild attacks of the influenza; also the fact that these cardiac manifestations, even when chronic, occur without any sign of disturbed circulation, without congestion of the liver or the kidneys, and without anasarca, which could hardly be absent with degenerative processes of the heart-muscle. In favor of the neuropathic nature of these severe cardiac manifestations after influenza is the fact that the frequent post-influenzal neurasthenia often seems to have a cardiac basis in that it is accompanied by marked subjective and objective cardiac manifestations (palpitation of the heart, heart anxiety, tachycardia, bradycardia, and arhythmocardia).

There are but few reports from competent pathologists on the pathologic changes in the heart; the most exhaustive are by Kuskow. Since influenza is generally fatal through inflammatory complications, especially from pneumonia, the cardiac changes found are probably due to these rather than to influenza. The changes which occur are those usually found in acute infectious diseases,—that is, myocarditis,—especially parenchymatous and fatty degeneration, often combined with consecutive dilatation of the ventricle (Wallis, Marchand, Bollinger, Stewart, Kuskow). Lenhartz found in one case of influenza pneumonia combined with pleurisy and pericarditis, and several small metastatic abscesses containing streptococci in the heart substance.

Several cases of "primary" endocarditis verrucosa sive ulcerosa have been described by various authors as a sequel of influenza (Emminghaus, Fiessinger, Engesser, Gerhardt, Surmont, Pawinski, Teissier, Huchard, Hefforn, official reports from Switzerland and from Germany).

But the endocarditis is more frequently due to inflammatory processes in the lung and the pleura, and is the result of mixed infection, especially with streptococci, which were shown to be present in the vegetations by Oulmont and Barbier. Influenza bacilli have, up to the present time, not been found in them. Endocarditis following acute articular rheumatism complicating influenza ("synovitis grippalis") is repeatedly mentioned (Müller in Zürich, Swiss report), and especially often endocarditis pneumonica.

Cases of influenzal pericarditis with fibrinous or purulent exudate are reported from Bassi, Tyson, and in many official reports and collective investigations. But much more often pericarditis is a sequela of pneumonia, pleurisy, and the complicating acute articular rheumatism.

By analogy with the modern doctrine of "uremic pericarditis" it has also been assumed that the influenza toxin is capable of directly causing pericarditis, but it is not likely that the toxins do more than damage the tissues, and thereby facilitate the invasion by the specific inflammatory micro-organisms.

Hemorrhagic, serofibrinous, and purulent mediastinitis sometimes follow pneumonia, pleurisy, pericarditis, and gangrene of the lung, and have been observed in several cases by Krannhals.

An important and relatively more frequent sequela of influenza is phlebitis with venous thrombosis; of this there are numerous records in literature. It is unnecessary to give a list of the names of all the authors. In the official and private collective investigations of all countries this complication is noted, and accompanied by examples; the German collective investigation mentions 25.

The favorite seat of the post-influenzal thrombosis is, like in other infectious diseases and conditions of cardiac weakness, the veins of the lower extremities, particularly the femoral veins and the veins of the leg. Frequently the affection is bilateral and symmetric.

Although as a whole rare, yet relatively much more frequent than in other acute infectious diseases, is influenza thrombophlebitis affecting also the large veins of the upper extremities (brachial vein and even the axillary vein).

Another peculiarity of influenzal venous thrombosis is its not infrequent association with a mild and short attack of influenza. Naturally it occurs most often in severe cases, especially in those characterized by cardiac weakness and tachycardia, the "forme cardiaque" of influenza.

Another characteristic which we noticed in two cases of thrombosis of the veins of the upper arm is its very acute onset and progress. In a physician of Cologne, strong and in the prime of life, we saw, after a severe cardiac influenza, thrombosis of the veins of the upper arm, which, within twenty-four hours, caused a marked swelling and blue discoloration of the whole extremity. Possibly the acute character of the influenzal venous thrombosis explains the remarkable fact, repeatedly mentioned in the literature, that venous thrombosis had caused gangrene of the affected extremity. This, as is well known, hardly ever occurs in venous thrombosis, and one would be tempted to suppose that these cases resulting in gangrene were due to arterial obstruction, were it not that in some cases the affected extremity first became very swollen and edematous—a characteristic of venous obstruction.

In accordance with what has just been said above, is an observation by Johannsen (St. Petersburg). He describes a case of venous thrombosis of the right arm and leg. The latter became gangrenous. At the amputation of the thigh several veins were found filled with firm thrombi extending far up, while the femoral artery had only some slight atheromatous degeneration.

Cases of thrombosis of the cerebral sinuses are also on record. Especially characteristic of influenza, although of rare occurrence, yet observed relatively frequently, is the occlusion of larger arteries by thrombi. It has also been occasionally observed in other infectious diseases, especially after typhoid, but is extremely rare.*

Thrombosis as a complication was really first recognized in our recent pandemic, for, apart from a short note from the time of the epidemic of 1782 concerning "spontaneous gangrene of the extremities" following influenza, we do not know of any other mention in the early literature. Those from the recent epidemic are, however, extremely numerous. We would call attention to the reports of Senator and von Gerhardt (January 23, 1890), of von Leyden, Camerer, Georg Sydenham, Loison, Cathomas, Emminghaus, Eichhorst, Bondet, Duchesneau, Teissier, Hugh-Highet, Stevensohn, Steinegger, Wartenweiler, Vonmoos, Keller; furthermore, the German collective investigation, the collection of the official German reports by P. Friedrich, and the Swiss report by Schmid.

The occlusion generally affects large arteries, and is relatively often bilateral, affecting symmetric vessels. The popliteal artery is the one most frequently occluded.

In the eight cases of the German collective investigation the popliteal artery was affected five times; the femoral, once; the brachial, once; and the cerebral arteries once. The cases of Keller, Stevensohn, Cathomas, as well as Leyden's second case, were of the brachial artery. Emminghaus described a rare case of endaortitis with thrombus formation in the ascending aorta. The cases of thrombosis of the splenic artery (report from Hessen) and of the mesenteric artery, with necrosis of the intestine (Stevensohn), were probably of an embolic nature.

The signs of arterial occlusion are the ordinary ones: generally, severe pain; always, absence of pulse and coldness and anesthesia of the extremities; bluish-black discoloration, then dry gangrene, with mummification of the affected part; marked prominence of the cutaneous veins. If the thrombosis affects an easily palpable artery (popliteal, femoral, brachial), the thrombus can be recognized as a tough strand. The prognosis is naturally a very unfavorable one; even in amputated cases, death almost always follows. The arterial thrombosis frequently gives rise to autointoxication, which is caused by the absorption of katabolic poisons. There are the facial expression and color of the skin of septicemia, collapse, generally with hypothermia and great cardiac weakness, total anorexia, and delirium.

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* Compare the instructive article by von Leyden concerning arterial thrombosis after the acute infectious diseases, "Berlin. klin. Wochenschr.," 1890, 14.

The cause and etiology of the arterial occlusion following influenza are undoubtedly manifold.

Teissier and the French physicians speak simply of an "artérite grippale," similar to their "artérite typhoidique," applied to gangrene following typhoid, without entering upon any explanation of the process.

In a number of cases there may have been emboli, especially in those where arteriosclerosis of the aorta existed, together with acute or chronic endocarditis; and even in cases where gross pathologic changes could not be found or detected, thrombi may have become detached from the left heart.

Occasionally influenza may have been directly followed by senile gangrene, or influenza may have accelerated an arterial occlusion already prepared by an arteritis obliterans by its enfeebling effect upon the heart.

But even conceding all these possibilities, there still remain a large number of cases which can be explained only as cases of primary or spontaneous arterial thrombosis.

Von Leyden is disposed to connect the thrombosis with "the disintegration of the leukocytes, which are increased in number from the beginning of the disease up to and even after the fever crisis, and then give rise to much degenerative product." If these products of disintegration and the blood-platelets become deposited in large quantity on the arterial wall, they may give rise to the formation of an arterial thrombus. Von Leyden calls attention to the analogous formation of thrombi of blood-plaques in phosphorus, arsenic, and potassium chlorate poisoning; and the gangrene following carbon monoxid poisoning might also have been mentioned here.

Gerhardt, who observed a case of bilateral occlusion of the crural artery followed by gangrene of the toes on one side and the lower third of the leg on the other, is disposed to class such cases together with "symmetric gangrene," and believes that it is a spasmodic vascular contraction and "vasomotor gangrene," since there were in his case certain visual disturbances similar to those occurring in symmetric gangrene and dependent on spasm of the retinal arteries. But the symptom-complex of "symmetric gangrene" in the strict sense of the term is very definite. There is spasm only of the smallest arterioles, and the extremely slow progress of the dry gangrene remains confined to the tips of the toes and the terminal phalanges, and hardly ever spreads to the tissues higher up. Such a typical case following influenza has been recorded by Hugh-Highet in a girl twenty years of age, in whom the gangrene remained exclusively confined to the symmetric toes and terminated in recovery. The case of Petrina may be due to a similar condition of vascular spasm; this author observed alternating sensations of cold and warmth in one finger and one toe after influenza. I found in the literature but one case of typical "symmetric asphyxia" (Raynaud) occurring after influenza. It was reported by Le Joubioux, and occurred in a woman of thirty-five.

Regarding the condition of the blood in influenza, there are but few observations, and these by no means exhaustive.

Von Jaksch could find no changes in the blood; Klebs only a slight decrease in the red cells; Pribram only a decrease in hemoglobin during the period of convalescence. On the other hand, Schermer, in the clinic at Freiburg, found in a few cases within a few days a marked diminution of red cells and hemoglobin, while Renzi found a marked diminution of the latter with only a slight decrease in the number of the erythrocytes.

Chiari and Bäumler observed in several cases a remarkably large number of the so-called "degenerative bodies" in the blood; Klebs attributes to the "granule heaps" found by him a very important rôle in the influenza process, viz., the formation of capillary thromboses in various organs. (Compare p. 607.)

Increase in the white blood-cells—leukocytosis—was regularly observed even in uncomplicated influenza by A. Kollmann, P. Friedrich, Chantemesse, Laveran, Kartulis, Dannecker. On the other hand, Rieger (Munich) could never find leukocytosis in simple influenza even during high fever, nor in catarrhal influenza pneumonia, but he did find it in the true croupous pneumonia. *Adhuc sub judice lis est!*

Bäumler observed hemoglobinuria in one case—a unique observation in influenza literature.

Microcytes were frequently found by the same author during the febrile attack; they disappeared after it was over.

From these observations—marked decrease in hemoglobin; destruction of many red blood-corpuscles; urobilinuria and hemoglobinuria; alleged great frequency of icterus, which he considers to be hematogenic—Bäumler comes to the conclusion that "in influenza infection the blood undergoes fundamental changes in a very short time."*

We cannot entirely agree with this too dogmatic statement, and it has not been satisfactorily proved, for influenza in the great majority of cases is a very mild and harmless disease; but we do not wish to ignore the fact that one peculiarity of influenza, well known since the oldest times (Wittich, 1580), namely, a disposition to hemorrhages of various kinds, is very much in accord with this theory. We called attention above to the frequency of hemorrhages from the nose, gums, pharynx, and larynx, to the hemorrhagic bronchitis, the simple intestinal and renal hemorrhages, as well as menorrhagia and metrorrhagia; further, that the inflammatory processes in the serous and other membranes (leptomeningitis hæmorrhagica) of the brain (encephalitis hæmorrhagica), of the intestine and stomach (gastro-enteritis hæmorrhagica), in the middle ear and tympanic membrane (myringitis hæmorrhagica), had frequently a pronounced hemorrhagic character. We may further mention the frequent occurrence of purpura hæmorrhagica, the muscle hematomata found by Kuskow, and the complicated cases described by the same author under the name "hemorrhagic influenza," which were characterized by hemorrhages into various organs (muscles, dura mater, pia mater, bones, endocardium, lungs, stomach, intestines, etc.). Further, we may regard the degenerative bodies and granule accumulations described above, which were found in the blood by Klebs, Chiari, and Bäumler, as responsible for the venous and arterial thromboses and also, as Klebs especially points out, for the not infrequent termination of pneumonia in gangrene of the lung.

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* Many physicians of the previous century (Rutty, 1762; Fothergill, 1775) remark on the conspicuous yellow, often saffron-yellow, color of the serum in the blood from venesection.

Nevertheless, the hypothesis of primary "deep-seated changes in the blood in influenza" still requires considerable additional evidence.

The marked tendency to hemorrhage is simply explained by the "vasomotor" hyperemia which characterizes all the inflammatory phenomena occurring in influenza, and may easily give rise to extravasations without any necessarily severe change in the blood or without the capillary thromboses insisted on by Klebs.

A case of "acute leukemia" following influenza is described by Hinterberger, and a case of "acute pernicious anemia" by Rheiner.

There are but few reports concerning the condition of lymphatic glands in influenza. Meckel (Nuremberg) regularly found swelling of the cervical glands, and Schröder (Neustadt a. H.), of the cervical and inguinal glands. The German army reports note "lymphangitis" and "swelling of the lymphatic glands." The Swiss report mentions that swelling of the lymphatic glands was not infrequently observed. Zehn (Geneva) often found the bronchial glands swollen at the postmortem examination.

Inflammation of the thyroid, strumitis, followed sometimes by suppuration, occurs occasionally as the result of secondary infection in all acute infectious diseases, especially in typhus and pneumonia, and has also been observed on several occasions after influenza (German army reports, official Swiss report, Holz, and Gaucher).

SYMPTOMS REFERABLE TO THE GENITO-URINARY APPARATUS.

As far as the frequency of renal disease is concerned, influenza does not occupy any particularly prominent position in comparison to other acute infectious diseases. The influenza bacteria and toxins are by no means so dangerous to the kidneys as, for instance, the toxins of scarlet fever, diphtheria, pneumonia, erysipelas, and smallpox.

All the statistics reveal an infrequency of acute nephritis, and this accords also with the reports of numerous experienced observers.

Von Leyden mentions in detail but one case which, on postmortem examination, was found to be a typical glomerulonephritis. Mosler, Strümpell, Drasche, and Pribram each report but one or two cases of acute hemorrhagic nephritis. Senator observed it "a few times."

In the German collective investigation only 4.5 per cent. of the observers mention the complication of "nephritis and albuminuria." The German army report mentions, among 55,263 patients, but 10 with "severe inflammation of the kidneys."

Anton (Würzburg) found nephritis in 2 per cent. and Gmeiner in 1 per cent. of the cases; Gutmann (Nuremberg) saw but four cases of "genuine acute nephritis" (1.5 per cent.) among 262 patients.

Among the 439 influenza patients in the pandemic, we saw "acute hemorrhagic nephritis" but twice. But even at that time we called attention in our influenza lectures to the fact that during the months after the termination of the epidemic remarkably many cases of nephritis were admitted, without any etiologic history other than an antecedent attack of influenza. Perhaps these were cases of a post-influenzal nephritis analogous to those following scarlet fever, tonsillitis, and diphtheria.

Pathologic reports are naturally scanty (Wallis, Weichselbaum, Ribbert); they assign the nephritis partly to parenchymatous degeneration and partly to glomerular inflammation. Extensive necrotic processes were observed by Beneke and Kuskow; the latter also found numerous small purulent foci in the kidney, doubtlessly due to a secondary infection.

A transient, slight albuminuria, the so-called "febrile" or congestive albuminuria, is observed when there are diffuse capillary bronchitis and cyanosis, with pneumonia as a complication, or large pleural effusions, and in cardiac weakness. Many believe that this transient albuminuria is also due to the influence of the toxins.

Manassein, Zdekauer, Hermann and Socoloff, Engel-Bey* emphasize the great frequency of albuminuria in influenza. Teissier claims to have seen it in one-half of the cases, Grandes 23 times among 29 cases, and Senator 18 times among 52 cases—that is, in about one-third of the cases. On the other hand, Anton could find a slight albuminuria in but 5 per cent. of the cases, and Krehl in 3.5 per cent. According to the Swedish physicians (collective investigation), albuminuria "but rarely and transiently" occurred. As the result of our own observations, we agree with the last-mentioned authorities, who believe albuminuria in influenza to be of rare occurrence.

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* *Loc. cit.*, p. 47.

These diametrically opposed views regarding the frequency of albuminuria in influenza no doubt depend partly on the different methods employed for the detection of albumin.

Only serum-albumin and serum-globulin are of clinical significance —that is, in indicating renal mischief; albumose and nucleo-albumin, on the other hand, are not interesting, as these bodies in themselves may be. Fallacies may easily occur, as, for instance, in applying the boiling test with the addition of acetic acid (formation of soluble acid-albumin) or by applying the cold nitric acid test (precipitation of nucleo-albumin, which is mistaken for serum-albumin). The ideal method for the clinical demonstration of albumin is not that which demonstrates the presence of any proteid body (serum-albumin, serum-globulin, albumose, nucleo-albumin), but that which only shows serum-albumin and serum-globulin.

This is also the place to consider glycosuria and diabetes mellitus. The latter is frequently mentioned as a sequel of influenza (Rob. Saundby, Broadbent, Bouchard, Eichhorst, Rosenstein). Bossers quotes several cases from Dutch literature. A. Hennig claims to have observed diabetes frequently as a sequel of influenza. Fischl found transitory glycosuria often after the termination of the fever, and Frankhauser even states that he found sugar in the urine of all cases. Influenza may very likely have often caused the outbreak of a latent diabetes, and yet more frequently may a latent diabetes have become evident only from the fact that the attack of influenza led to an examination of the urine. [Schwarz saw glycosuria occur with post-influenzal neuritis. Both symptoms improved together. Glycosuria may recur with a second attack of influenza and then persist.—Ed.]

The unfavorable influence of influenza upon an existing diabetes is emphasized by Kahler, Drasche and Féréol, and others. Especially dangerous to diabetics was diffuse capillary bronchitis or pneumonia.

Cystitis was observed occasionally after influenza, as after other acute infectious diseases. Cases of "retention of urine for several days" (Ehrenhaus, Bilhaut), of "vesical paralysis" (Swiss reports), of vesical spasm, cystodynia, enuresis nocturna, following influenza belong to the extensive domain of influenza neuroses.

Goldberg observed "complete and sudden recovery, after influenza, from a post-gonorrheal cystitis that had existed for one and one-half years." He thinks it possible that the influenza toxins eliminated in the urine may have exerted an inhibitory action upon the microbes of chronic cystitis. On the other hand, three patients of Trossat, with chronic catarrh of the bladder, had an acute attack as a consequence of the influenza.

As far as the chemic condition of the urine, apart from albuminuria, is concerned, there are but scanty and unimportant reports. No exact metabolic experiments were made during the influenza period. The rapid and important losses in weight mentioned above (p. 667), even in uncomplicated cases of influenza, point to deep-seated metabolic disturbances.

The reports about the quantity of urine, its specific gravity, uric acid and urea elimination, acidity, and the increase in phosphates, emphasized by many authors (Huchard, on the contrary, found them decreased), contain nothing worthy of detailed mention here. There is nothing unusual in the fact that, in a disease like influenza, which is frequently accompanied by high fever and profuse sweating, the quantity of urine may be so decreased that anuria lasting from twelve to sixteen hours may occasionally occur (Alison). Bäumler found urobilinuria in many cases, Alison frequently, and Hayem in all cases; Hayem considers this symptom characteristic of influenza. The tests for the detection of urobilin are now so delicate that urobilin can often be demonstrated in the urine of healthy individuals.

Albumosuria and peptonuria were frequently observed (Dochmann, Hofmeister, Meixner, Alison), which is not surprising considering the frequency of purulent inflammations in the lung, bronchi, and pleura. Indican in the urine was often observed by Senator and Gautrelet. The Ehrlich diazo-reaction was never found by Goldschmidt and Bäumler, but frequently by Senator and Gutmann, sometimes as marked as in enteric fever.

Simple hemorrhage from the bladder (Swiss report) and also simple hemorrhage from the kidney were observed by Leyden, Fräntzel, Bernhard, Eichhorst, Krannhals, Engel-Bey, and others.

The present specializing age has produced an extensive literature on the influence of influenza upon the female sexual organs. The principal points can be easily rendered in a few words, and agree entirely with the reports of observers of the earlier epidemics, from the fifteenth to the eighteenth century.

The following facts have been established: The influenza attack very often gives rise to a premature menstrual period, and occasionally causes its recurrence after it has normally ceased a few days previously. The menses are often unusually profuse, and may sometimes increase to true menorrhagia. In some women who have already passed the climacteric there occasionally occurs, as I can confirm, renewed unexpected hemorrhages from the uterus as a result of influenza (Pipingsköld).

Of more importance is the well-known fact, mentioned in older works on influenza,* namely, that influenza often leads to abortion. This undoubtedly occurs much more frequently as a result of hemorrhages into the membranes than, as has been supposed, of any oxytocic influence of the influenza toxins.

Abortion, judging from the reports, occurs equally frequently at all periods of pregnancy; it occurs most often in severe attacks of influenza, particularly in those complicated by diffuse capillary bronchitis, dyspnea, cyanosis, spasmodic attacks of cough, and especially in those complicated by pleuropneumonia. Abortion occurring during influenza pneumonia makes the prognosis considerably more grave. The hemorrhages occurring from abortion are sometimes of an alarming degree.

The experience of some large lying-in institutions, that, in spite of the extensive infection of influenza, no premature births occurred, does not in any way overthrow the fact, established in the history of influenza from the earliest epidemics to the present day, that influenza very frequently causes premature births. This appears also, as we have shown above (p. 568), from the marked decrease in the birth-rate during the months following the pandemic.

But the assertion, based on very doubtful statistics, that pregnant women are especially predisposed to influenza, lacks all foundation.

As far as the male genital organs are concerned, simple influenzal orchitis is the most frequently mentioned (Dind and Roux in Lausanne, C. Barnes, Jozèfowicz, Fiessinger, Scheller, Zampetti). Kottmann reports a case terminating in suppuration, and Büngner a similar case terminating in gangrene of the scrotum. Walker describes a case of "suppurative periorchitis with gangrene of the testicle." Cases of "gangrene of the penis" are reported by Johannsen and by Devrient.

The English influenza epidemics, 1732–1733 and 1737–1738, were characterized by a frequency of complication with "inflammations of the testicle and parotid," which makes one think that the influenza epidemic was accompanied by a concurrent epidemic of parotitis with frequent secondary infections. In the English epidemic of 1580 the frequency of parotitis is also mentioned. (Compare p. 671.)

AFFECTIONS OF THE SKIN AND LOCOMOTOR APPARATUS.

The redness of the skin, mostly combined with hyperidrosis, is generally considered an important symptom of influenza, and is interpreted as an angioneurosis (vasomotor paralysis) due to influenza toxins. We have remarked above that this hyperidrotic redness of the face, combined with spasmodic cough, forms an important point of differential diagnosis between the croupous influenza pneumonia and the genuine form.

Frequently the redness of the skin appears in the form of a marked scarlatiniform or measly eruption, particularly on the face, forehead, chest, and other parts of the trunk; frequently also on the upper extremities, more rarely on the lower. Very often the face shows a mottled redness, so that the external appearance of many patients, with their conjunctivitis, coryza, and cough, vividly reminds one of a case of measles, and that, although the eruption existing has the characters of the initial rash of scarlet fever—fine, flaky, closely aggregated, and not raised. Teissier describes a series of cases in which the differentiation between his "scarlatiniform" and "rubeolar" form of influenza and true scarlet fever or measles was difficult.

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* "Par la véhémence de toux plusieurs femmes grosses acouchèrent avant la terme" (Pasquier, 1410); "Abortions and death of childbed women were common" (Th. Short, 1517).

The above-described measly and scarlatiniform erythemata, to which may be added urticaria (R. Guiteras's "influenza erythematosa"), occur most frequently during the initial stage and at the height of the disease; they are generally of short duration, sometimes very transitory, and are only occasionally followed by desquamation. It is not improbable that the scarlatiniform or measly eruption may often have been due to the influence of drugs, especially of antipyrin.

Krannhals and Fräntzel observed scarlatiniform eruptions, urticaria, erythema nodosum, and herpes zoster to arise even eight to fourteen days after the termination of influenza. The toxic origin of this late rash presents no difficulty of explanation, since we know that with the antidiphtheria serum the eruption often does not appear until eight to ten days after the injection. A similar explanation holds good for the late appearance of nephritis.

It was the frequency of these eruptions which gave rise to the erroneous supposition at the beginning of the pandemic of 1889 that the disease was dengue fever; for in the latter the eruption is a pathognomonic sign.

In the following paragraphs we will mention a few of the rashes observed in influenza, but without laying claim to an exhaustive description.

Herpes was frequently seen on the usual sites (lips and nose). Teissier terms it, "extremement fréquent." Schulz and Demuth found it in 25 per cent. of the cases; Krehl, in 12 per cent.; Bristowe and Petersen, each in 10 per cent.; Stintzing, in 8 per cent.; Anton, in 6 per cent.; and Preston, in 5 per cent.

We found herpes only in 4 per cent. of the cases, namely, out of 105 cases complicated with pneumonia, in 5 per cent.; out of 334 uncomplicated cases, in 3 per cent. Herpes undoubtedly occurs less often in influenza pneumonia, and particularly in the croupous variety, than in the genuine croupous pneumonia.

Teissier describes herpes of the tongue. Herpes zoster of the chest or other portions of the body is frequently mentioned (Real, Dodler, Kollmann, Bilhaut), and particularly as a sequel of influenza following on intercostal neuralgia. (Compare p. 639.) Herpes iris and circinnatus were frequently observed (Schwimmer). Of the erythemata, besides the ordinary forms already mentioned, measly and scarlatiniform eruptions, together with urticaria and roseola, were seen (Teissier, Curschmann) in 1.2 per cent. of cases; further, erythema papulatum (Hawkins, Béla Medvei, Moore, Bristowe), *erythema nodosum*, and *erythema multiforme*, with or without affection of the joints (R. Guiteras, Schwimmer).

Mention of facial erysipelas complicating influenza is found fairly often, even in the accounts of the older epidemics (1775 and 1847–1848 in England). It has often been noted together with parotitis. No doubt it is due to a secondary infection with streptococci. In the last epidemics this complication is recorded by Laborde, Heller, Helfer, W. Bennet, Lemoine, Mason, Mayor, Schmid, Camenzind, Schmidlin.

Simple and hemorrhagic pemphigus is mentioned several times in the Swiss reports as sequelæ of influenza. Purpura hæmorrhagica was also of frequent occurrence (Landgraf, Pribram, Locke, Drasche, Ewald, Senator, German army report, Swiss report). Pick (Prague) and Fleury (Switzerland) each describe a case of fatal purpura with general hemorrhagic diathesis.

It is hardly surprising that in a disease accompanied by such profuse sweating as influenza extensive miliary eruptions (cristilina rubra) are not rare.

Purulent forms of dermatitis (folliculitis suppurativa, impetigo, multiple furunculosis, ecthyma) have been frequently observed as sequelæ of influenza. Léloir considers that his "Pyodermites acnéiques et seborrhéiques influenciques" may be the result of infection in two ways: either by direct inoculation of the infectious nasal secretion upon excoriated skin areas, or, endogenously, by the elimination of the microbes in the blood through the glands of the skin. The erythematous forms are most simply classified among the toxic eruptions.

Among rarities and curiosities belonging to the trophic disturbances of the skin we may mention cases reported by Rosenstein (Leiden) and by Sympson, of vitiligo (leucopathia acquisita). Further, "acute grayness of the hair of the head within a few days" (Bossers in Leyden), premature grayness of the eyelashes (Bock), and finally a case of alopecia areata following influenza (Williamson).

The statistics concerning the frequency of the exanthemata in influenza will vary much according to whether herpes is included or the general vasomotor redness of the skin is designated as erythema.

We found a "finely punctate eruption" altogether in 9 per cent. of cases; in the face alone, in 6 per cent. Exanthemata in the more restricted sense of the term were found by Hawkins in 1 per cent.; Guttmann, in 3 per cent.; Comby, in 6 per cent.; Barthélémy, in 7 per cent. of the cases. Bristowe observed erythematous rashes in 6 per cent. of the cases, a papular or scarlatiniform rash in 20 per cent., while Preston found a papular rash in 2.3 per cent. of the cases.

The study of the history of influenza teaches us that, like most of the symptoms, the various skin eruptions were known to the older influenza writers.

Herpes is mentioned in one place by Wittich (1580): "On some of them there was an eruption on the point of the nose which formed a scab." Slevogt mentioned herpes in 1712; Blass in 1772; Gray in 1782.

Concerning the "rash of scarlet eruption," mention is made by Whytt (1758), Heberden (1775), and Hamilton (1782).

Fr. Hoffmann (Berlin) mentions "urticaria" even in 1729, as well as the miliary eruptions and purpura hæmorrhagica.

We may again emphasize at this point, having the skin manifestations of influenza under consideration, the increased sweat secretion, combined with the "vasomotor" redness of the skin, as a characteristic sign of influenza ("grippe sudorale") by a few authors. Peters describes hyperidrosis universalis as an obstinate sequela of influenza.

All acute infectious diseases are occasionally followed by polyarthritis. Influenzal synovitis is of extremely rare occurrence.

It is certainly far more rare than the synovitis of scarlet fever and epidemic cerebrospinal meningitis. It is not mentioned at all in the hospital statistics from Hamburg, Leipsic, Munich, Würzburg, nor in the statistics of Bristowe, Preston, Robertson, and Elkins. Senator and Holmberg each report but one case. In the large German collective investigation only 7 per cent. of the observers reported polyarthritis. Among the 55,263 cases in the German army, 44 cases of articular rheumatism were attributed to influenza. In our influenza lectures we reported 6 cases from the first pandemic. All these influenza synovitides were mild and of brief duration, analogous to the true synovitis of scarlet fever and cerebrospinal meningitis. We may also call attention to the rarity of polyarthritis in influenza in contrast to its frequency in dengue fever.

As regards the muscles, we have drawn attention above to the violent myalgias. Annequin describes cases of "myositis" or "neuromyositis"; Bossers, a peculiar case of permanent contracture of numerous muscles, in which a chronic fibrous myositis was supposed to have been the cause. Multiple abscesses of the muscles, doubtlessly due to secondary infection, were found by Kohts; Kuskow found extravasation of blood into the muscles in three cases; in many cases he found finely granular cloudiness with partial loss of the transverse striations.

Apart from empyema of the pleura, antrum of Highmore, and the frontal sinus, the surgeons often had opportunity of seeing the effects of influenza in some rare affections of the joints, bones, tendons, and upon neuroses.

Witzel, Krönlein, and Walker observed cases of acute suppurative inflammation of the knee-joint which, in the first case, was due to a "mixed infection with the Streptococcus pyogenes." Early during the pandemic of 1889 Möser described two cases of periostitis of the upper jaw in direct relation to influenza. Periostitis and ostitis were observed also in other bones, especially the tibia and fibula. Böse describes a case of purulent periostitis combined with superficial ostitis necroticans of the tibia in a young, healthy man.

As characteristic of influenza painful inflammation and thickening of the plantar fascia ("fasciitis plantaris") are mentioned. It reminds one of the extremely painful plantar neuralgias following enteric fever.

J. Franke has compiled the surgical literature on this subject in the "Archiv für klinische Chirurgie," 1895, vol. xlix.

The unfavorable influence which influenza exerts upon surgical patients, especially those operated on or injured, as well as upon "old inflammations, especially in bones," was mentioned by several authors (Verneuil, Lücke, and Walker). Verneuil advises the postponement of every non-important operation during an influenza epidemic.

DISEASES OF THE EAR AND EYE FOLLOWING INFLUENZA.

It is not our intention to enter into a detailed consideration of the special literature on diseases of the ear and eye following influenza. As far as diseases of the eye are concerned, important and voluminous accounts of a particularly rich variety of diseases exist.

A glance at the statistics from the practice of the specialists, both private as well as hospital and outpatient cases, shows an enormous increase in disease of the ear during the period of influenza and immediately following it. From them one might imagine that influenza attacks the organ of hearing with an enormous frequency beyond all other infectious diseases. But it is evident that these statistics of a special branch of medicine merely emphasize the enormous morbidity of influenza.

According to the reports of large general hospitals, otitis as a complication of influenza plays only a minor rôle from a statistical point of view. These general statistics represent the true relative frequency of this complication, even admitting that many cases of ear and, we may add, many cases of eye disease arise only during the period of convalescence—that is, after the discharge of the patient from the hospital.

The following figures will convey some idea of the frequency of otitis:

Of the 3185 contributors to the German collective investigation, 1209 (or 38 per cent.) mention complication with diseases of the ear. Among the 55,263 influenza patients in the German army, disease of the ear was observed in 0.5 per cent. of the cases. Among 30,000 patients in Strassburg, Jankau found diseases of the ear in 0.5 per cent. We* observed otitis media with perforation of the tympanic membrane in 2 per cent. of our cases. The Swiss report contains the statistics from the practice of a number of physicians (not specialists). They saw otitis media in 2 per cent. of 1508 influenza patients.

We will confine ourselves to a simple enumeration of the most important diseases of the ear.

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* Influenza lectures, p. 35.

As in all infectious diseases, the middle ear is especially liable to invasion by the specific bacilli and their products by way of the nasopharyngeal space. Otitis media terminating in suppuration and perforation of the tympanic membrane is by far the most frequent disease of the ear in influenza.

Suppuration from the ear as a sequel of influenza is first mentioned by Huxham (1729), although the report of Wittich (1580), "Some clamored about the pain in the ears," may be interpreted as referring to otitis.

The inflammation frequently assumes a hemorrhagic character. The intense hyperemia of the mucous membrane of the tympanic cavity and the tendency to hemorrhage and veritable hemorrhages from the ear are universally emphasized by all observers.

In the purulent secretion of otitis the ordinary pyogenic organisms, and especially the Diplococcus lanceolatus, have been found. Scheibe succeeded, in 1892, in demonstrating the bacillus of Pfeiffer in the discharge.

The extension of the purulent inflammation to the mastoid occurred but rarely in comparison with the total frequency of the influenza otitis, as Keller and Auerbach rightly point out.*

We may further mention myringitis, which frequently showed a marked hemorrhagic character, giving rise to the formation of ecchymoses, hematomata, and blood-blebs (M. bullosa).

Otitis externa with the formation of blood-blebs upon the surface of the auditory passage was repeatedly observed.

We know of but one observation, and that by Lannois, concerning primary or secondary disease of the labyrinth terminating in deafness as a sequel of influenza.

Influenza did not influence the deaf-mute statistics.

The prognosis of influenzal ear diseases is a very good one—considerably better than when following scarlet fever, epidemic cerebrospinal meningitis, enteric fever, and small-pox.

Worthy of mention are the not infrequent aural neuralgia, hyperesthesia, and tinnitus aurium.

To meningitis and pseudomeningitis of otitic origin we have alluded above (p. 651).

As we have mentioned above, there is a very extensive literature of the most varied forms of diseases of the eye following influenza.

Nevertheless, apart from simple conjunctivitis and the associated diseases of the lids, the actual frequency of influenzal and post-influenzal diseases of the eye is remarkably small. Even the specialist statistics of the large eye clinics and polyclinics have not reported any appreciable increase in the number of ocular diseases during the time of influenza.* We will here only enumerate the observations, without giving the names of the numerous authors.

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*Collective investigations of Cologne (influenza lectures, pp. 36, 37. Nevertheless, the reports of the specialists concerning the frequency of purulent mastoiditis are very contradictory.

Affections of the conjunctiva (hyperemia, inflammation) are by far the most frequent in influenza.

Differences in the definition of conjunctivitis have caused great differences in the statistics. Thus Stintzing found 159 cases of "inflammation of the conjunctiva" among 405 influenza patients. Comby found but 10 among 218 patients. Robertson and Elkins (Edinburgh) observed conjunctivitis in 71 per cent.; Preston, on the other hand, in only 16 per cent. of the cases.

Accompanying the conjunctivitis, as in any ordinary cold, edema of the lids and chemosis of the conjunctiva frequently exist. But O. Rosenbach believes that "edema of the eyelids" may be a diagnostic sign in itself in influenza—that is, in an epidemic period.

The "moist, watery luster of the eye" is considered by many to be characteristic of influenza. Great stress is laid on the "watery eyes" in the English collective investigations. Bristowe found it in 96 per cent., and Anton (Würzburg) in 68 per cent. of the cases.

In some cases the edema of the lids was followed, through mixed infection with pyogenic cocci, by abscess of the lids. There occurred also subconjunctival and episcleral ecchymoses, inflammations of the caruncle, the semilunar folds, episcleritis, catarrhal and purulent dacryocystitis.

Of much greater interest are the diseases of the cornea, notwithstanding that they belong to the rarities. Among the 55,263 soldiers of the German army that were ill with influenza, inflammation of the cornea was observed only in three. Mention may be made of the varieties noted by the specialists, namely, "keratitis punctata superficialis," herpes of the cornea, and keratitis dendritica or sulcata.

The last-named affection of the cornea, of which but a few cases had until then been observed, was seen and described during the influenza period remarkably often by many. It appears from the third to the seventh day of influenza, and undoubtedly stands in causal relation to the latter. Some assume that it is due to an invasion by the influenza germs into the lymph-spaces of the cornea. The process, which is said always to occur unilaterally, is very protracted and not seldom results in permanent corneal opacity. The disease consists of a central bleb, from which dendriform arborizations extend, consisting either of opaque corneal tissue or of sulci with opaque floor; together with this there are only slight irritation, anesthesia of the cornea in the region of the area of dimness, slight photophobia, and moderate pericorneal injection. This influenza keratitis is also deserving of notice in that it resembles somewhat another infectious disease of the cornea, the malarial keratitis of Kipp, with which it seems to be clinically identical.

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* Compare Ruhemann, *loc. cit.*, p. 147.

Of the other diseases of the cornea, there were also observed post-influenzal parenchymatous and hypopyon keratitis.

Of the diseases of the eye observed during and after influenza, we have yet to add: hyperemia of the iris, plastic iritis, iridochoroiditis and cyclitis, suppurative choroiditis terminating in purulent panophthalmitis, and phthisis bulbi; also fresh vitreous opacities and hemorrhages into the vitreous. Acute and occasionally even hemorrhagic glaucoma was repeatedly observed. Retinal hemorrhages and detachments of the retina and embolus of the central retinal artery have been described; also thrombosis of the retinal arteries, analogous to the previously mentioned arterial thromboses of the extremities (Dujardin). Pflüger, Bergmeister, Schöler, Snell, and Hardy report papillitis, neuroretinitis, and optic neuritis; Pflüger, Gutmann, Ruhemann, Bergmeister, and Eperon mention retrobulbar neuritis. Retrobulbar hematomata with exophthalmos are also mentioned.

Of the affections of the orbit, there occur: Inflammation of the capsule of Tenon, suppurative tenonitis terminating either in recovery or purulent panophthalmitis.

Of the affections of the sensory ocular nerves, we may mention photophobia, retinal hyperesthesia, and especially the frequent pain in the eyeball extending deep into the orbital cavity (neuralgia of the intra-orbital branches of the trigeminus).

The many paralyses of the internal and external ocular muscles have been extensively considered in the section on Influenzal Neuroses. (Compare pp. 641 and 642.)

We are still quite in the dark concerning the pathogenesis of the numerous ocular affections just mentioned (whether due to influence of the toxin or invasion by the specific bacilli). The majority of the inflammatory processes, with the exception of the regular conjunctivitis, are probably, especially in the severe purulent conditions, due to a mixed infection with the ordinary pyogenic cocci. The presence of Pfeiffer's influenza bacillus has not yet been demonstrated in ophthalmic practice.

Undoubtedly, numerous diseases of the eye which occurred after recovery from influenza have, in the absence of other etiologic factors, through the vague etiology of many ocular diseases, been erroneously attributed to influenza, with which they had either but slight or no causal relation. [Anemia also occasionally follows influenza.—Ed.]

THERAPY OF INFLUENZA.

In a disease like influenza, so intimately connected with human intercourse and commerce, whose germs are carried with the utmost rapidity to all quarters of the compass by innumerable persons, provisions for general prophylaxis are practically impossible. By no known measures could a people be safeguarded against an influenza epidemic. Only shipping can, under some circumstances, be put in effective quarantine. The prohibition of landing from ships which had influenza patients on board is said to have prevented the introduction of influenza into Australia in 1891, and into the harbors and coast cities of several West Indian Islands in 1890.

On account of the observations made in several countries, especially in England, that the fairs and markets were evidently the points from which the pestilence was carried into all directions, it was proposed to prohibit officially, at the time of an epidemic, all large meetings, exhibitions, fairs, markets, pilgrimages. The "world pestilence influenza" will not be in the least diminished by such precautions. The prophylactic closing of schools is also of no use, as the children remaining at home or playing in the streets have ample opportunity of acquiring influenza as easily as at school, even admitting that the schools are the principal points from which the disease is spread. (Compare p. 570.)

The adherents of the miasmatic theory, who cling to the idea that the atmosphere is the focus and the medium of transmission of influenza, justly discarded, from their standpoint, all measures of isolation and disinfection. "To do such things," says Ruhemann, "is merely beating the air." But when these "miasmatics" gave the "natural advice" that "the individual should expose himself as little as possible in the open air, since those were first and most affected who were compelled by their occupation to remain for a long time in the open air," they revealed a remarkable conception of the nature of the air contained in our living rooms, as if it were hermetically, or at any rate microbically, sealed from the air outside.

It was only after recognition of the contagious nature of influenza that the question of individual prophylaxis could be more closely approached. The answer was simply as follows: He who is able to isolate himself from human intercourse, to prevent every contact with influenza patients, or with persons having to do with influenza patients, has to some extent a guarantee, similar to those inmates of certain prisons and strictly closed convents, of escaping influenza. Since these conditions are scarcely possible to the ordinary mortal, the only course left for the "influenzaphobe" is flight into a district free from influenza. In isolated local epidemics these precautions may lead to the desired end; pandemic influenza will pursue and surely overtake the fugitive.

In the household and in the family the attempt may be made, by strict isolation of the patient, by disinfection of his sputum, his handkerchiefs, his body- and bed-linen, eating utensils, floors, and furniture, to render the germ which has found its way in harmless for the rest of the family. But at the height of a pandemic such prophylactic measures have not the slightest hope of success, because the members of the household are exposed to numerous other opportunities for infection.

In closed institutions, prisons, lunatic asylums, hospitals, especially upon ships, such isolation and disinfection measures have better opportunity to achieve a result and are often of actual use. For barracks too the order of the French Ministry of War, "especially to isolate every slightly affected patient from communication with the other soldiers," is fully justified.

In order to disperse the indifference and slight attention paid to influenza at the beginning of the pandemic, an attempt was made to give "public instruction" on the subject. A circular from the Minister of the Interior in Baden of December 19, 1889, not only described the manifestations of influenza and its dangers by the association of pulmonary inflammation, but also gave details regarding the treatment, and advised affected persons to keep in bed, to observe a restricted diet, to employ diaphoretic teas, to take a purgative, to abstain from cold compresses, and to envelop the head in warm cloths or cotton wool. "If the symptoms become more severe, one should not delay to call in medical assistance."

From the fact that the upper portion of the respiratory tract is the principal point of location of the influenza germs, it was advised, in order to prevent infection, to employ disinfecting washes several times a day for the mouth and throat, and also nasal irrigations or sprays, insufflation of menthol, etc. For inhalation many English physicians strongly recommended oil of eucalyptus; others advised creolin, camphor, and oil of peppermint. Cleansing of the mouth and throat can do no harm, but nasal irrigations may give rise to irritation of the mucous membranes and hyperemia, and thus create a predisposition to a successful invasion by the influenza germs. Ruhemann even believes that the nasal mucus acts as a "trap for influenza bacilli," and that the underlying mucous membrane may thus be protected from the germs, and, therefore, the mucus is not to be forcibly removed. It is unfortunate for this theory that the influenza bacilli thrive so excellently upon mucus.

Finally, proposals were not wanting to fortify, or even immunize, the body against the influenza germs by the use of certain drugs, etc.

The harmless cod-liver oil recommended by Ollivier, the calcium sulphid so praised as a prophylactic by Green, and many other panaceas have been rightly discarded.

Gräser in Bonn, in the beginning of the epidemic of 1889–1890, upon the basis of very doubtful theoretic assumptions, asserted and maintained, even subsequently, that "quinin given at the proper time and in proper doses is capable of preventing the outbreak of an attack of influenza."

The members of one troop of the Bonn hussars regiment had daily doses of 0.5 gm. of sulphate of quinin in whisky for three weeks. This troop, in comparison with others, had a very small number of influenza patients. I regard this as mere coincidence, and as little convincing as the experiment carried out by Tranjen in a similar manner in a battalion of infantry in Sistova (Bulgaria). Nor does the latest communication by Sinclair-Coghill convert us to the hypothesis of the prophylactic action of quinin. We share the opinion, expressed in the German army report, which says that "from a single such experiment no conclusions can be drawn." The prophylactic action of the quinin is exceedingly questionable. The cadets of the military school in Glogau regularly had quinin administered to them in wine, "and without the slightest success," for this military school was visited by a very severe epidemic (German army report). Spillmann (Nancy) also did not observe the slightest result from the prophylactic action of quinin. Of 14 persons who took daily doses of 0.5 gm. quinin, 12 had influenza, no milder than the average.

Mosse endeavored to solve the question of the prophylactic immunization by quinin by experiment. He injected blood from influenza patients, or pure cultures of Pfeiffer's bacillus, into the vein of a rabbit's ear. One-half of the animals experimented upon had a dose of quinin (0.05 gm.) intravenously injected, and the same quantity per os one-half hour before the experiment was made. These animals remained well, whereas the animals that did not have quinin administered became ill. It is unfortunate for these experiments that even R. Pfeiffer himself has not been able to produce influenza in animals. The assumption that the animals were found immune when injected with influenza cultures, together with their toxins, in the experiments just mentioned, because the previous administration of quinin had rendered the toxins innocuous, and, as it were, neutralized them, rests upon so feeble a basis that we need not waste more words on it.

The *a priori* assumption that quinin, being a bactericidal agent, would diminish the virulence of the influenza bacillus and thus mitigate and shorten the course of the disease, gave rise to an extensive use of this remedy during the influenza epidemic of 1889 in France, and especially in Russia, where quinin became the popular panacea, as did with us antipyrin. The sale of quinin increased in St. Petersburg to an almost incredible extent (Heyfelder).

Opposed to those extolling quinin, viz., Rawlins (1833), Carrière, Teissier, Gellie, Bubrulle, Briard, Pribram, and especially Gräser, who speaks of its "specific action" in influenza, are van den Velden (1874), Eichhorst, Tranjen, and Bowie, who saw no good result from the remedy. We unhesitatingly agree with the latter. Quinin manifested its antipyretic properties in the fever of influenza, and influenced some neuralgias during the period of convalescence even more favorably than its modern competitors, but on the influenza process as such it had not the slightest effect. The results of our trials with quinin we summed up in the following words in 1890: "The cases treated with large doses of quinin have regularly felt more ill than those who have not been treated by quinin (increase of headache, etc.). Experience thus shows that as a prophylactic quinin is valueless."

Putting together the considerable material available from the official reports from the whole of Germany, P. Friedrich says that certain physicians praise the brilliant results obtained with quinin, while others were very much disappointed in this respect.

Treatment by purgation, which under the influence of the teachings of Brown during the influenza epidemic at the end of the eighteenth century attained a great reputation, also in our day found some few to praise it. Calomel in purgative doses (Schuster, Dumas) and large doses of castor oil (Sagorski, Mosler) were said to have an abbreviating influence on the attack of influenza. Really to prove this would not be easy.

It is only in the purely gastro-intestinal form of influenza that laxatives and intestinal disinfectants, especially calomel, could possibly have an abortive action. That purgatives must be cautiously administered is self-evident when we recollect the above-mentioned severe hemorrhagic forms of influenzal enteritis. The advisability of giving a mild laxative at the onset of a disease in constipated patients is obvious.

A large number of medicaments and other materials were credited, purely empirically, with an effective or "specific" action in influenza.

To these belong ammonium chlorid, especially praised in France; furthermore, benzol, benzonaphthol, carbolic acid, creasote, creolin, turpentine, ichthyol, balsam of Peru, cinnamic acid, tannin, potassium iodid, corrosive sublimate, double chlorid of gold and sodium, sulphid of calcium, sulphocarbolate of sodium, carbonate of potassium, aconite, gelsemium, tinctura cardui Mariæ, etc.

For credulous therapeutic optimists, disposed to consider all favorable terminations of disease in the light of *post hoc ergo propter hoc*, influenza was an excellent case, since the enormous majority of attacks terminate favorably and spontaneously in a few days.

The most fortunate are the "homeopaths"; for here too, as in every other disease, or for every symptom of the disease, they possess also for influenza a specific infallible remedy. We do not begrudge them their wonderful recoveries any more than we do their companions, "the nature doctors," "magnetopaths," etc. The supporters of Kneipp, of course, praise their water douches and their adjuncts, camomile tea and Kneipp coffee; the vegetarians commend their diet; the adherents of Jaeger, their woolen clothing—as the safest protection or remedy against influenza. Voices have also been raised for the use of suggestion and hypnosis in the treatment of influenza.

There is neither a prophylactic nor a specific for influenza. The hope that some day it may be possible to immunize, by preventive inoculation with a future "influenza serum" on the approach of an influenza epidemic, and to treat the patients in a truly specific manner, is to-day no mere fantastic speculation, although it must be admitted that such hopes, especially as regards influenza, must be deemed very remote, if only for the reason that influenza is a disease which arouses interest often only at intervals of several decads.

In Madeira during November, 1889, there was a severe epidemic of small-pox, for which numerous revaccinations were performed. At the beginning of 1890 influenza was brought into the country and quickly disseminated by a lady coming from France. It was very striking, Goldschmidt reports, that all those successfully vaccinated (112 in number) remained unattacked by influenza, while of 98 others who were unsuccessfully vaccinated but 15 were affected. Goldschmidt, therefore, supposes that vaccination confers a protection against influenza. Althaus has made the same observation. With this the problem of general "preventive vaccination" is solved, although by a means in most vivid contradiction of our conceptions regarding natural and artificial immunization.

The treatment of influenza in the absence of a specific remedy can be only symptomatic. It is directed, therefore, to the relief of the most prominent symptoms, clinical conditions, and complications. The enormous area covered by the protean symptomatology of influenza affords many opportunities for the beneficial treatment of patients, partly also by the use of drugs. Naturally we cannot here enter upon the innumerable variations in therapeutic treatment suitable for each individual case, and we, therefore, must confine ourselves to a few salient points.

In the great majority of cases, beyond rest in bed and restricted diet, advisable also in mild cases, and the ordering of certain hygienic measures affecting the comfort of the patient, no further, and particularly no drug, treatment is necessary.

The consensus of opinion that influenza should be treated by warmth is nearly unanimous. As a matter of fact, all experience seems to indicate that cold applications are generally not well borne and increase the discomfort. Many recommended, on the first indication of the attack, immediately taking a hot bath or a Turkish or Russian bath, or enveloping the patient in blankets or giving hot drinks (elder tea and decoction of lime blossoms) to cause thorough diaphoresis (Rosenbach, Frey, Eichhorst, Laffont; compare also the report of the ministry at Baden, p. 169).

The advice given by a celebrated hydrotnerapist that the patient should immediately, on the first indication of influenza, take violent muscular exercise—*e. g.*, a walk of several hours—until he perspired thoroughly, shows but little experience with influenza. In the great majority of cases influenza comes on suddenly without any premonitory symptoms, and the patient is neither inclined at this stage nor is he capable of walking for any length of time. In "influenzaphobes" without influenza such advice may sometimes have had a wonderful suggestive effect.

I have also considerable misgivings concerning the treatment by vapor baths of every stage of the disease (Frey). Such procedures at the height of influenza only increase the fever, intensify the already discomforting sweating and headache, and have a pernicious influence upon the general condition of the patient. All cases of influenza that are at all severe object energetically to the vapor baths. Washing with lukewarm water, on the other hand, with or without the addition of alcohol, lukewarm baths (as consistently ordered by Manassein), the wet pack, and sitz-baths (Mettenheimer) may occasionally be of use. The adoption of any hard-and-fast rule is to be deprecated.

Although supporters of the cold-water treatment in most acute infectious diseases, we abandoned it in influenza, finding that so far from attaining any improvement in the headache and other neuralgic pains or of the nervous prostration, we obtained rather the contrary effect. The annoying cough, diffuse bronchitis, dyspnea, general hyperidrosis, and the often-existing cardiac weakness are contraindications to the cold bath. Even cold applications and ice-bags to the head were often and regularly refused by the patient as being useless and increasing the pain.

Of great use, and frequently indicated on account of the severe nervous manifestations during the influenza attack, are certain sedatives and antineuralgics which, although they do not have any specific influence upon the influenza, nevertheless produce favorable effects. First among these stands antipyrin.

No sooner had the "specific therapeutic power of antipyrin in influenza" been advertised at the beginning of the pandemic of 1889 than a regular rush was made for the remedy, which at that time could still be bought over the counter. In small places, where the stock of antipyrin was soon exhausted, there were even hostile demonstrations by the populace against the drug-stores. Every one who had influenza or thought he had it, and many who wanted to protect themselves from the disease, took antipyrin *ad libitum.* No doubt harm was done by this foolish abuse of the remedy, especially by large and long-continued doses. Nevertheless, assertions that antipyrin "caused the death of many influenza patients by cardiac paralysis," and was the cause of the frequency of influenza psychoses, are exaggerations.

Only lack of experience or preconceived prejudice can doubt that antipyrin prescribed at the right time in proper doses is often of great use for the severe neuralgias and myalgias and the general hyperesthesia and insomnia, both at the acme of the disease as well as at its onset, and often gives at least transitory rest to the much-burdened patient without doing him the slightest harm.

Phenacetin acts much the same as antipyrin. Antifebrin is of much less value. Eichhorst, Drozda, Turner, Heubner, and others especially praise the antineuralgic and sedative action of salicylic acid. Schäffer observed immediate improvement in the pains of the head, back, and legs from the use of sodium benzoate.

The success of antipyrin and salicylic acid led to the commercial production of a mixture of the two—salipyrin. It would have been remarkable if this mixture should not have produced the same results which each of the component parts showed. It was at once lauded to the skies as a specific remedy.

Hennig, one of those especially praising the remedy, remarks: "After a dose of from 3 to 5 gm. of salipyrin, given during a period of one to three hours in an afternoon, one sees the nervous phenomena, the fever, and the prostration disappear; the patient passes a quiet night, and upon the following morning is often completely restored to health," which in our opinion in such a case would have happened without the use of salipyrin. Among the chief eulogists of salipyrin are some of whom one may assume with certainty that their clinical experience of influenza was insufficient to justify their giving an opinion.

Salipyrin was immediately followed by migrainin, salophen, and other compositions with similar recommendations as specifics. [Many eminent physicians obtained excellent results by the administration of quinin, and several consider it to be preferable to any other drug.—Ed.]

As regards the treatment of the severe neuralgias, especially of the headache and the nervous jactitations at the height of the attack, we have often seen, as already mentioned, useful results from the careful administration of the above-named sedatives (antipyrin, phenacetin, salicylic acid, and salipyrin). In the stubborn neuralgias during the period of convalescence the use of quinin must also be considered; we agree entirely with the experiences of Curschmann and Bäumler that "the tried drug quinin is in many cases of subsequent neuralgia more effective than its modern competitors, and is frequently useful when they have failed."

The inflammatory pains of pleurisy, the spasmodic attacks of cough, the dyspnea and distress of the patient occasionally reach a degree in which the previously mentioned sedatives are useless, and opium or morphin must be resorted to. The fear of its "paralyzing action upon the heart" of the latter, the anxiety that the first injection of morphin is at the same time the first step to morphinism, is very wide-spread but without foundation. We have repeatedly seen, after a sufficient injection of morphin, the severe attacks of cough and the pleuritic pains become much milder, the excited respiration become quieter and deeper, and, as a result of this, the circulation improve and the pulse become stronger. I might relate here the clinical history of a physician who suffered from a severe attack of cardiac influenza, in whom anginal attacks were severe and of long duration, which nothing relieved so much as injections of morphin. It was with hesitation at first that we gave them, but after each injection the respiration became quieter and the pulse, which had become imperceptible, returned.

The good results obtainable from the moderate administration of opium were observed even in the earlier epidemics by Nelson and Pearson (1803), and in the most recent pandemic by Brown and Noé. But it should not be given as a matter of routine.

The use of morphin, sulphonal, and trional should generally be withheld in the insomnia of influenza, since the disease lasts only a few days. In cases of severe agrypnia following influenza it is often impossible to do without these drugs.

Only in rare cases does the pyrexia itself require interference; generally in those where the temperature remains on a high level and the patient is suffering visibly thereby. Antipyretics, by decreasing the temperature, often improve the general condition of the patient as well as the condition of the pulse and the elimination of urine. In seeking this antipyretic result the chief rule to be observed is to give the smallest dose of the drug that is necessary to produce its antipyretic effect and keep the temperature on a lower level.

The routine administration of antipyrin every two hours in doses of 2 + 2 + 1 gm. is, curiously enough, taught even to the present day by some medical authorities. It is only this totally misguided application of the remedy that has discredited modern antipyretics. Many cases with high fever can have their temperature reduced to the desired level by 0.3–0.5 gm. of phenacetin or lactophenin, or by 0.3–1.0 gm. of antipyrin. Consequently the variations in temperature must be studied in each case during the administration of antipyretics.

During the administration of antipyretics the temperature should be regularly taken, at least every two hours, so that the administration may not be unnecessarily continued. Febrile temperatures which remain refractory against 0.5 gm. phenacetin, 1.0 gm. of antipyrin, or 2.0 gm. of quinin, as notably in some hyperpyrexial cases, cannot be suitably treated by antipyretic drugs.

Acting according to these principles, we have for some time found the previously mentioned antipyretics extremely efficacious and quite harmless. We cannot, however, as the result of daily experiences at the bedside, agree with the modern conception of the favorable influence of high body temperature upon the course of the disease. On the other hand, we are just as opposed to the maxim, "Febris est delenda."

Alcohol in most cases of influenza increases the headache. Those patients who ask for and feel themselves strengthened by alcohol should not be refused wine and brandy. In the treatment of the cardiac weakness the alcoholic stimulants are of great use. At the beginning of the last pandemic it was stated, especially by French physicians, that alcohol, particularly in the shape of hot drinks, would produce protection against influenza—a view quite devoid of foundation.

The advice to be particularly careful during convalescence, not to get up too early nor to leave the room, to guard against catching cold in order to escape relapses or complications with pneumonia and pleurisy, should be strictly followed.

We cannot here further consider the symptomatic treatment of influenza, particularly the innumerable manifestations of the disease referable to the nervous, respiratory, and circulatory apparatus; still less the large number of complications and sequelæ. We must refer our readers to the respective sections in this work.

LITERATURE.

The literature of influenza is extraordinarily voluminous. Since the last pandemic of 1889 it has assumed enormous dimensions, developed in the medical journalism of all civilized countries. We shall limit ourselves, therefore, to drawing attention to the more important articles and to such communications as bear special relation to our treatment of the subject.

The extensive special literature on eye, ear, surgical and gynecologic diseases, as well as the psychoses resulting from influenza, will not be considered in detail.

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DENGUE.

DENGUE.*

DENGUE fever† has several epidemiologic and numerous semiotic characteristics in common with influenza, so that in former times the question was raised whether both diseases were not varieties of the same species.

In Paris, even at the time of the outbreak of the influenza pandemic in 1889, an animated discussion arose as to whether the disease were influenza or dengue. As a result of this numerous opinions were given which decided upon the identity or the close relation of both diseases, declaring that dengue was "a tropical variety of influenza"—a great mistake, for only in a few symptoms is there any analogy; in well-marked cases of both diseases they are throughout very different and do not give any occasion for confusion. Dengue is a specific infectious disease *sui generis*, which has nothing in common with influenza.

Since the influenza pandemic of 1889 the interest of the European physicians in dengue also has been aroused, so that a comprehensive review of this disease, especially upon the basis of our latest experiences, since it has been brought appreciably nearer to us by the epidemic of the year of 1889, will be opportune. Dengue, epidemiologically considered, is one of the most interesting infectious diseases; for while it is generally conceded to be contagious in a high degree, communicable through commerce and especially through shipping, yet up to the present time it has been confined almost exclusively to tropical and subtropical regions. The principal area of distribution in which the disease has been observed lies between the tropic of Capricorn and the tropic of Cancer, and the contiguous districts of the temperate zones. Only transitionally has the disease appeared once as far north as 40° (1780, Philadelphia); in 1889, in Constantinople (41° N. Lat.), and perhaps in Varna (48.2° N. Lat.), while it hardly ever appears to have overstepped the equator in a southern direction further than the tropic of Capricorn (southern point, South Paolo in Brazil, 23.2° S. Lat.).

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* It should be remembered, in reference to the remarks on the etiology of dengue in this article, that it was written before the publication of Ross's researches on malaria and the discoveries which have arisen therefrom.—ED.

† The present description of dengue differs considerably from those usually found in the text-books up to the present time. It makes a claim not only to have made use of the important and critical experiences of the latest epidemic, which occurred partly in Europe, in 1889, but also to give a complete clinical epidemiologic picture of the affection according to our present knowledge.

The remarkable progress which the pestilence made in the unusually hot summer of 1889 (Constantinople, Salonica) shows that the coast of the European Mediterranean is accessible for the entrance of dengue fever under favorable conditions. But when, on the strength of this fact, von Düring says, "the assumption that climate acts as a barrier to dengue is no longer tenable," we cannot agree with him. Dengue now, as before, still remains a disease of the tropical zones and the adjoining temperate areas, and only exceptionally has it extended further and reached Philadelphia in 1780, Cadiz and Seville in 1784, Constantinople and Varna in 1889.

These facts, like many others in geographic pathology, are of great general significance and should teach modesty to the extreme contagionists. I refer to those who think the course of epidemics can be explained by the increase of the germ in the body of the patient, their excretion, so to speak, by the patient and by the direct contagion from person to person—viz., by an exclusively endogenous hypothesis, while ignoring the exogenous temporal and localizing factors or depreciating their value. The last factors, as we shall see later, play an important rôle in dengue fever.

NOMENCLATURE.

Opinions regarding the etymologic origin of the word "dengue" diverge considerably. According to some learned investigations, the word is of old Arabic origin, and signifies "asthenia" (Vambery), while others derive it from the East African word "*dinga*," or from the Indian "*dangue*"; both expressions signify "blow," and perhaps are intended to designate the sudden onset of the disease. Probably, however, the word is of Spanish origin, and of similar significance to the contemporaneous expression, "dandy fever." ("*Dengue*," prudishness, affectation; "*denguero*," affected; affected, "dandy-like.") Both expressions describe the peculiar tortuous, affected gait which the patients adopt in consequence of the pain and motor disturbances in the knees and ankles. The same symptoms are referred to in the names "polka-fever" (Brazil), "pantomime fever" (English colonies). From these pains in the knee-joints and bones dengue gets the names "broken wing," "breakbone fever" (America), "knockelkoorts," ankle fever (Dutch colonies), "abou-abous," "abou-rekabe," knee pain, "père des genoux," "des massues" (Arabia, Syria, Egypt, Tripoli). On account of the great and protracted weakness which follows the disease it was called in Philadelphia "break-heart fever"; while, on account of its mildness, it obtained the name "la piadosa," "the mild," in Spain. The expression "trancaze" points to the sudden "apoplectiform" beginning of the disease. On account of the accompanying exanthem dengue received the designations: "Fiévre rouge" (Syria), "calentura roja," "rosalia," "colorado," "giraffe," "bouquet "(viz., mottled). Its regular occurrence at the time of the date harvest gave it the name of "date fever" in Port Said and Arabia. Very characteristic is the name of "three-day fever" formerly in use in India.

All these expressions are not the result merely of a play of words, and they point to very significant and especially to historically important characteristics of the disease.

GEOGRAPHIC DISTRIBUTION OF DENGUE AND THE MOST IMPORTANT EPIDEMICS.

1779–1800: The first reports concerning dengue originate from the year 1779, during which it was observed at Java (Batavia), and about the same time at Cairo and Alexandria. During the years following, the reports of epidemic outbreaks accumulated. The disease prevailed in 1780 upon the coasts of Coromandel, of Arabia, and Persia.

Even at that time the disease made an isolated excursion over the subtropical zone, and during the hot summer of 1780 broke out suddenly in Philadelphia (40° N. Lat.).

During the year 1784 it appeared for the first time in Europe with epidemic outbreaks in Cadiz (36.5° N. Lat.) and Seville (37.5° N. Lat.). Most probably the disease was carried thither by troopships which came from the West Indies. A second epidemic broke out in Cadiz in 1788. At the end of the previous century dengue was reported from Grenada (Lesser Antilles).

1818: Epidemic in Lima (Peru).

1824–1828: With the years 1824–1825 a geographically extensive period of dengue begins, which gradually spread over a great portion of the tropical and subtropical zone.

Great epidemics on the western coast of Farther India (Rangoon) and on the eastern coast of India (Calcutta, Madras) ushered in this period in 1824. Soon the disease showed itself in Suez, on the sea-route from India.

In the years 1826–1828 dengue spread itself in extensive epidemics over the greater portion of West India, the Virginian Isles, and the Greater and Lesser Antilles (Havana, 1826; St. Thomas, 1827).

From here numerous coast towns of Central America and of the most southern portion of North America and the most northern portion of South America were attacked (Havana, Charleston, New Orleans, Vera Cruz, the coast of Florida, and Venezuela). Isolated cases are alleged to have been observed at that time in New York and Boston, and notably again in Philadelphia, among the crew of a ship coming from Cuba.

1830–1870: During these four decads dengue is met with in large and small epidemics at numerous places in its tropical and subtropical area of distribution. The principal sites of the disease were:

Numerous coast towns of India (1830, 1835–1836, 1844–1847, 1853–1854).

Tahiti and other South Sea Islands (1852–1853).

The coast of Arabia and northern Egypt (Alexandria, Cairo, Port Said).

The principal epidemic years here were 1835–1836, 1845, 1868. Furthermore:

Tripoli (1856), Cyprus, and Syria (1861).

Réunion (1851), Zanzibar and Madagascar (1864), Senegambia and Greece (1845–1848, 1856, 1865), the Canary Islands (1856).

Numerous West Indian Islands (1860–1863).

Central America, especially New Orleans, Savannah, Charleston, Iberville, New Iberia, Georgia and Louisiana, Mobile, the coast of Texas and Ohio (1839, 1844, 1848, 1850).

South America, Peru (1852), and Rio de Janeiro (1846–1848).

In Europe: Cadiz (1863, 1867).

Two facts stand out during this period in the geographic distribution of dengue. To begin with, its first important appearance in South America, namely, in Rio de Janeiro, where from 1846–1848 the disease prevailed yearly "on water and on land" during the hot season (December and January), and each time with considerable severity. Secondly is to be noticed that, during this period, Europe was twice attacked, and, as on the previous occasions of 1784, so too in 1863 and 1867, the harbor city of Cadiz in southern Spain became the center of an epidemic, which in both instances was brought in by troops returning from West India, the home of dengue. From Cadiz the disease spread to Xeres, Seville, and a few other cities of Andalusia, but the north remained exempt; in fact, in Spain, as a whole, the disease remained insignificant.

1871–1873: A very extensive outbreak of dengue occurred in the years 1871–1873, when it appeared first on the East African coast (Zanzibar), then on the Arabian coast (Aden, Jiddah, Mecca, Medina, and Tanyef), and in Port Said. From here it was carried by an emigrant steamer to Java, from Aden by a troop-ship direct to Bombay, Kananur, and Calcutta. Following on this it spread through the countries of the Indian Ocean, Hindustan, especially in Calcutta and Madras, Rangoon, China, Formosa, Java, Celebes, and Sumatra. The last appearances in this important epidemic period occurred on the Persian coast, in the islands of Mauritius and Réunion, situated on the coast of eastern Africa, and, furthermore, in Tripoli and Senegambia. In the same year, 1873, epidemics took place in the southern portion of North America bordering on the Gulf of Mexico, Louisiana, Alabama, etc.

1876–1888: During the year 1876 there was an epidemic in Hong-Kong. During the year 1878 the disease was brought to Ismailia (Suez Canal) by a pilgrim ship, and from this place it traveled to Alexandria and up the Nile. In the same year Malta was also infected by a troop-ship from India. We further add: 1880, the ports of the Red Sea, especially Jiddah; 1880–1881, Cairo; 1881: Khania, to Crete and Syria; 1885–1886: the Fiji Islands; 1887, Gibraltar; 1888: Cyprus, and in the same year "whole Virginia" (Charlottesville).

Within this period fall numerous epidemic outbreaks in Syria, especially in Beirut, where, according to de Drum and Suquet, no fewer than fourteen epidemic years could be counted from 1861 to 1889.

1889: Of particular interest is the considerable distribution of dengue immediately preceding the influenza pandemic of 1889; in Syria and Palestine, in Asia Minor, Cyprus, Rhodes, Chios, and the islands of the Archipelago; furthermore, in Cairo and Ismailia. The disease spread "with incredible rapidity," and attacked now for the first time Damascus and Jerusalem.

From Beirut, Smyrna and Maghnissa were infected, and from the latter place Constantinople, and soon afterward the port of Piræus and Athens. From Constantinople the disease was carried to the Pontine southern coast (Trapezunt) and to Varna and further still to Salonica.

On this occasion dengue continued even into the cool season (November), and in some places was almost continuous with the succeeding influenza. To this fact much importance must be attached; for if influenza and dengue were identical diseases, as they have so often erroneously been maintained to be, they would not have succeeded each other in such a short time—in Constantinople, Athens, and Salonica. But since dengue is a specific infectious disease *sui generis*, it also did not render the inhabitants of these cities immune against the approaching influenza coming from the north. Also in the Fiji islands in 1885 there existed an influenza and a dengue epidemic closely following and even overlapping each other.

1890–1895: During these periods only a few epidemic outbreaks are known. They affected Senegambia (St. Louis) in 1890, in 1893 the East Indian fleet, and in 1895 Hongkong.

EPIDEMIOLOGY AND ETIOLOGY.

The just described, precisely considered and for the first time concisely arranged tabulation of the greater known epidemics teaches us important epidemiologic features of dengue. In order to complete the picture it would be necessary to compare the relations between individual epidemics. We will present only the most important facts, which, for the sake of brevity and clearness, we will arrange under the following heads:

1. Dengue is a disease of the tropical and subtropical regions, and within these zones it has a marked preference for the hot season —for summer. The disease almost always ends, as if suddenly cut off, on the occurrence of colder weather or the commencement of the cool seasons. Nevertheless, it is not probable that the restriction of dengue to the tropics is due only to the higher atmospheric temperature; yet nothing is known of any influences due to other cosmic relations, such as dryness or dampness, vegetation or soil. It is worthy of notice, however, that the occasional trespass into the tem-

perate zones—*e. g.*, to Philadelphia in 1780 and Constantinople in 1889—generally occurs in unusually hot summers.

2. Dengue is a disease of the sea-coast, ports, and coast cities. From the coast it occasionally also extends up the large navigable streams, such as the Ganges and Indus in India, the Mississippi in America, the Nile in Egypt, and the "White Streams" in the Fiji Islands. This regular adhesion of the disease to the sea-coast and river-banks—yellow fever behaves in a precisely analogous fashion—shows that the shipping traffic determines, in the first place, the distribution of dengue. The disease generally has its limit where marine intercourse ceases. Only rarely and with difficulty, and then only for short distances, does it penetrate into the interior of a country by the main roads. Only once for a short time did the disease follow the railroads in India, extending from Calcutta to Umballa and Ludiana on the Panjab frontier. No doubt this characteristic of dengue is due partly to the fact that in the tropics the principal mode of communication is along the sea-coast. Influenza, too, although affecting both land and sea in the tropics, was confined principally to the chief trade ports. (Compare p. 539.) But it is not traffic alone which limits dengue to the sea-coast. There are undoubtedly yet other factors: local conditions found on the coast, especially favorable to dengue. It is perhaps on account of the decreasing warmth of the atmosphere that dengue does not rise to any altitude. In Réunion, one of the favorite foci of dengue, the cooler, higher lying portions of the island, although in constant communication with the shore, remained almost entirely exempt in all the epidemics. The same was noticed in Cuba, Jamaica, Martinique, and almost everywhere. In Lebanon dengue never extended higher than from 300 to 400 meters above the sea-level, but in the particularly hot year of 1889 the disease exceptionally reached places on Lebanon from 1200 to 1500 meters high, being brought there from Beirut (de Brun, Mahé). On the other hand, in Turkey in 1889 the disease remained limited, in spite of the coastal communication with the interior, to the coast around Constantinople, to the summer residences on the Bosphorus and in Asia, and to some parts of the Black Sea and to Salonica, once again following the old rule of remaining strictly limited to the sea-coast; we would again point out the complete analogy to yellow fever.

Regarding the epidemic of 1889 in Constantinople and the vicinity von Düring says: "All the ports in active communication with each other became infected, in a sequence practically corresponding to the activity of the traffic between them."

3. Dengue is to-day considered a "highly contagious" disease. Its whole manner of distribution as regards time and place and the numerous examples of its conveyance by marine intercourse confirm the assumption. The disease has been repeatedly carried from continent to continent and from coast to coast by pilgrim, emigrant, and troop-ships; from India to the Arabian and Egyptian coast, or vice versâ; from West India to the coast of America, to Alabama, South Carolina, Louisiana, Venezuela, Texas, to the Bermuda Islands, and even to Philadelphia and Cadiz in Spain.

In 1885 the Fiji Islands became infected from Numea (New Caledonia) by a European with dengue who had been permitted to land. In 1893 the whole East India fleet was infected by one ship, the "Boadicea," which had been infected with dengue in Bombay.

There can be no doubt that dengue appears in any place where it has not previously occurred only if imported. Moreover, there exist numerous reliable observations showing that dengue, imported into a house, barracks, a ship, or a fort by a single patient, causes immediate further infection and gives rise to an epidemic. A number of observations made by de Brun in Syria during 1889 show clearly how the disease, carried by a patient into a family, house, or village, led to continuous distribution by contagion, and to convection of the pestilence to a distance by the mails and caravans and to the neighboring Lebanon villages.

A number of analogous and striking examples proving the direct transmission from person to person have been partly observed and partly collected by von Düring and Mordtmann.

There can nowadays be no doubt that dengue patients give off the specific germ, and that this germ may, in favorable circumstances, directly infect others. Formerly a purely miasmatic conception of the disease was accepted.

Nevertheless, the whole series of epidemiologic facts indicates that contagion alone, in the strict sense of the term, cannot satisfactorily explain either the geographic distribution of dengue or the occurrence of the larger epidemics at the point of outbreak, or the local manner of distribution and the *en masse* infection. Consequently this matter is not so simple as modern extreme contagionists would have us believe.

The exclusive limitation in itself of dengue to the tropical regions and their vicinity and the restriction of epidemics to the hot season show that in the occurrence of an epidemic external exogenous phenomena play an important part. Were dengue as contagious as small-pox, scarlet fever, measles, and the pandemic influenza, it would long ago, like them, have extended itself over the whole earth and over all the zones.

The local theory of dengue is supported by its limitation to the sea-coast, to river-banks, and to ships.

The observations that have been made in Cuba, Jamaica, Martinique, Réunion, and almost everywhere that dengue, in spite of active communication between the affected coast places and the interior, was not conveyed to the latter; that inhabitants of the interior frequently contracted dengue at the coast, but on their return home did not spread the disease (in the interior itself epidemics but rarely occur)—led the older observers to an anticontagionistic and strongly local view. They inferred that the occurrence of epidemics (both the endemics as well as those which occur after the importation of the germ) was dependent upon local conditions, and that the disease did not spread itself in an exclusively contagious, but chiefly in a miasmatic, manner, in that the exogenous germs having reached a place and there multiplied, stamped that place as a dengue spot, where any one might contract the disease without coming in contact with a dengue patient.

This same theory applied to yellow fever is the one at present most in favor for that disease. [Thus in 1895—but now, ten years later, transmission of yellow fever by the mosquito is generally accepted.—Ed.]

In favor of this opinion is the fact of sudden multiple infection, and, in possessing this characteristic, dengue, like influenza, differs markedly from other exclusively contagious diseases. It can hardly be denied that this fact is more easily explained by a local miasmatic hypothesis than by the assumption of dissemination of the disease exclusively by contagion from person to person.

Although we must admit that the suddenness of multiple simultaneous infection, as in influenza (compare p. 544), is frequently only apparent, because the first cases escape observation, nevertheless we must not—although very customary nowadays—regard this rapid affection of the masses simply as an error of observation. Are we to believe that the excellent observers of earlier dengue epidemics in the West Indies, and especially those in India, Egypt, and Rio de Janeiro, who give evidence of the rapid distribution of the pestilence, with drastic examples, were mistaken and overlooked the gradual development of the pestilence? We have already discussed this question in the article on Influenza, and have explained this rapid affection of the whole population—denied in error—by the supposition that the influenza germs had become aërodromal and had caused simultaneous infection in great numbers among the people. So in dengue a general vehicle (air, water) probably causes the distribution of germs at the site of the epidemic outbreak.

Examples of the behavior of dengue just discussed are found in literature in great numbers. We would refer to those of A. Hirsch,* and may mention, from the excellent reports of Lallemant (Rio de Janeiro), that the crews of ships, as a rule, were suddenly and simultaneously taken ill, and that frequently several laborers on the same job, either unloading or loading, became affected by dengue in the same manner.

In confirmation of the just-mentioned "local" hypothesis is the fact that under unfavorable external conditions—*e. g.*, outside of the tropical zone, in Philadelphia and Cadiz—dengue spreads but little. In the first-mentioned instance the disease remained confined to a particularly dirty portion of the city (Front Street) before it became further distributed. It therefore obtained the name "Front Street fever." The "local" theory is further supported by the fact that dengue, even in its tropical home, frequently remains for a long time confined to certain areas—for instance, those near the ports or in localities with unfavorable hygienic conditions and in overpopulated portions of the city—before it becomes generally distributed (thus in St. Denis, Réunion, Calcutta, etc.).

In Constantinople, too, the disease first occurred in the dirtiest portions of the city—Kassin-Pacha, the chief focus of all epidemics and particularly of cholera. Mordtmann calls attention to the fact that numerous washerwomen live in this quarter who attend to the laundry of incoming ships. In Hong-Kong the disease prevailed in 1895, principally among the Chinese that were surrounded by unfavorable hygienic conditions. Exceptions to this rule are remarkably rare. Yet in Hong-Kong during the epidemic of 1876 it is alleged that the most favorably situated, sanitary, and new portions of the city were those chiefly affected.

Mordtmann in Constantinople reports that dengue prevailed most intensely in the most filthy quarters; in the summer quarters of the Bosphorus the cases that were imported frequently remained isolated. He calls attention to the analogy with cholera, and very correctly concludes that "for the occurrence of secondary outbreaks after the importation of a primary case certain favorable conditions are required."

The observers of earlier epidemics, from 1827 to about the beginning of the eighties, thought, indeed, that dengue was an "importable" disease, but that it was principally miasmatic—that is, an infectious disease dependent upon time and place. Later, and especially in the great epidemic of 1889, the opinions of strict contagionists gained the upper hand (Zülzer, de Brun, von Düring). Yet there were always objectors, like A. Hirsch and Wernich of earlier times, to the exclusive contagionistic teaching—*e. g.*, Chrysochoos during 1889 in Smyrna, Gaskalis and Orenstein in Greece.

It is very interesting to note the opinions of those investigators who saw epidemics of dengue and influenza occurring in quick succession at the same place, and were thus able to draw comparisons between the manner of distribution of both diseases. These observers are of the unanimous opinion that contagious dengue adheres to the coast and penetrates with difficulty and slowly, or even not at all, under the ordinary conditions of little inland communication into the interior. Influenza, on the other hand, a miasmatic disease, carried by the air, spreads itself with the greatest rapidity equally over city and country, over a whole island or continent, without any difference between coast and interior.*

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* *Loc. cit.*, p. 48, 55.

I am convinced that the reverse is the case. The highly contagious influenza extends with great rapidity wherever an infected individual is found; the far less contagious, but markedly localized dengue fever remains confined to its locality (sea-coasts, ships) and extends with difficulty into the interior, because the local conditions there for the exogenous propagation of the germs are ordinarily not so favorable as on the sea or river coasts.

Very interesting are the most recent reports of Skottowe on the dengue epidemic of 1885–1886 in the Fiji Islands. The introduction of the disease into Numea (New Caledonia) was due to the fact that an infected European was permitted to land. The time required for the disease to extend over all the various inhabited islands (about 80) was from May, 1885, to March, 1886. Everywhere the places on the coast were first affected; then the pestilence spread up along the river-bank. The distribution into the interior was slow and sparse. Just before and just after the outbreak of dengue there was an influenza epidemic, and thus one could, states the observer, recognize the great difference between dengue and influenza. The latter became disseminated, like the wind, over all the islands,—"justifying the hypothesis of atmospheric transmission,"—while dengue, on the other hand, as a contagious disease, remained confined to the coasts and became distributed only moderately and slowly toward the interior. The comparison is interesting, but the explanation is incorrect, as we have shown above.

In explaining the different mode of distribution of dengue and of influenza, there is one factor which deserves greater recognition than has been accorded to it up to the present time. The dengue patient, even in the mild cases, on account of the articular pains, is generally immediately confined to the bed and to the house, while innumerable influenza patients continued their journeys to all quarters of the compass and thus carried the germs to all parts with great rapidity.

The difficulties in explaining the various epidemiologic relations in dengue are lessened and the contradictions resolved if we assume that dengue, although under certain conditions a disease directly contagious from person to person, nevertheless is also dependent upon conditions of time and place in so far as the development and increase of the contagion outside of the human organism are concerned. This process is at present elastically termed "miasmatic." According to this definition, dengue would, therefore, belong to the contagious-miasmatic diseases. [Graham has described a parasite, resembling Pirosoma, in the blood of cases of dengue fever. According to him, the disease is transferred by the mosquito *Culex fatigans*, and he has been able thus experimentally to convey the disease. The parasite passes through a sporing stage in the mosquito in an analogous manner to the malarial parasite.—Ed.]

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* Zülzer writes: "Dengue is preëminently characterized by its contagiousness; it is infectious in the true sense of the word, and that apparently in an even higher degree than typhus or small-pox. Influenza, on the other hand, is not contagious." Von Düring: "Dengue is exquisitely contagious but influenza not so."

We will now consider some other important epidemiologic characteristics of dengue:

1. The contagium, the *materies morbi*, is unknown, but is undoubtedly of a microparasitic nature.

The meager bacteriologic investigations made up to the present time have yielded no result. The elements found in the blood by Cunningham and Charles (1873) and by Laughlin (1886) scarcely deserve mention. Experiments on transmission to animals were negative; only Vodermann claims to have obtained positive results in the ape. As of influenza, it has also been asserted of dengue, that it can be transmitted to dogs, cats, and other domestic animals. Especially in America whole herds of cattle are said to have contracted the disease (with paralysis of the posterior extremities). Our remarks regarding the supposed identity of influenza in man and the horse (p. 587) are applicable here too.

Nothing is known regarding the mode of entry or exit of the contagion nor of its mode of transmission. (Carried by air, perhaps also by water?)

2. There is no definite proof of the transmissibility of the germs of this disease by merchandise. The fact that dengue, a fever of short duration (three to seven days), was in earlier times, when ships were slow, nevertheless carried to some distances, from India to Aden, Suez, and Port Said, from the West Indies to Cadiz, when the ships' crews were undoubtedly free from infection after the lengthy voyage, is partly in favor of its transmissibility by merchandise, linen, etc.

Zülzer pointed out that the long-continued, branny desquamations of dengue convalescents is to be kept in view as a factor in the transmission of the disease. In the opinion of several physicians in Smyrna, the disease was imported by rags, which had been imported by the Hebrew rag-pickers yearly into Smyrna from Palestine, Syria, and Cyprus. The Greek government therefore forbade the importation of rags from

Smyrna into Greece. Von Düring quotes the following as an example: "A laundress, with the dengue eruption still on her, washed, ironed, and glossed the linen of five families. In each one of these families a member contracted the disease, and on each occasion that member who had used this clean linen; moreover, these were all individuals who, a few weeks previously, when the epidemic was in that quarter, had remained exempt.

3. The incubation period in dengue, as in influenza, is very brief, varying from twenty-four hours to a few days.

The period of incubation in the epidemic of 1889 in Constantinople was generally forty-eight hours. The shortest was twenty-four hours, and the longest probably not more than four to five days (von Düring). This was also the case in Athens (Orenstein). In earlier epidemics a longer period of incubation was noted—generally four days (Cotholendy, 1873, at Réunion; Burnett, 1872, in Bombay). Skottowe and Corney (the Fiji Islands, 1885) found the period of incubation a little over twenty-four hours; the observer of the epidemic in Hong-Kong (1895) mentions that the period of incubation was generally less than twenty-four hours.

4. There is a general consensus that one attack of dengue does not protect against a second attack. De Brun in Smyrna states that "there is no acquired immunity and that frequently the same individual is attacked twice during the same epidemic; some individuals even appear to have a predisposition, and have one or two attacks in each epidemic." According to von Düring, on the other hand, reinfections were of rare occurrence in Constantinople, but frequent, it is alleged, in Ismailia (Sandwith) during 1883.

At the same time there cannot be the slightest doubt that dengue confers immunity for a long time in the vast majority of persons. There is an analogy here to influenza, in which the frequent relapses and recurrences gave the impression of fresh infections, and gave rise to the erroneous teaching regarding the increased predisposition after one attack. (Compare p. 577.)

Mordtmann speaks of numerous second attacks and of cases in which dengue even occurs for the third time in the same individual (after three and six weeks). On the other hand, Skottowe often saw a remittent course, but never true reinfections.

5. Enormous morbidity with very slight mortality characterizes dengue just as influenza.

In St. Denis (Réunion), during 1873, 20,000 inhabitants out of 35,000 were affected, and during 1873 in Ismailia 1800 inhabitants out of 2000. In St. Thomas, during 1827, the whole number of 12,000 inhabitants are said to have been attacked; and in 1871, of the 900 men in the garrison at Aden, no less than 700 contracted the disease. In the last great epidemic of the year 1889, 90 per cent. of the inhabitants in Cairo and Ismailia contracted dengue, and in Smyrna 100,000 persons—that is, four-fifths of the inhabitants—were attacked. The usual estimate of the incidence, both in the older and in the more recent epidemics, is 75 to 80 per cent. De Brun thinks many millions were affected with dengue during 1889 in Syria, Asia Minor, Palestine, Greece, and Turkey. Von Düring, speaking of the distribution of dengue in Constantinople in 1889, says that "it was marvelous," and that four-fifths of the population were attacked.

6. The duration of the epidemic varies with the development of the disease. The more acute its form, the more rapidly does it spread, and the shorter is its course. The average duration of an epidemic is from two to five months; in the latter case the very late, straggling cases are often counted as belonging to the epidemic.

Everybody contrasts the long duration of the "contagious" dengue with the brief six to eight weeks' duration of the supposed "miasmatic" influenza. But this is correct only for pandemic influenza; the endemic forms in the year 1891–1892, as is well known, lasted in many places for several months. (Compare p. 548.) This could also be the case with dengue. The important part played by communication can, for example, be seen in that dengue required from May, 1885, to March, 1886, to spread over the numerous Fiji Islands; and also among the scattered inhabitants in Inner Samarant (1872) dengue spread but slowly.

7. In many spots in its tropical and subtropical area of distribution dengue is an endemic disease which may at any time appear autochthonously. As we have seen above, at certain times greater epidemic disseminations occur in numerous localities of the tropical zone, epidemics either independent of one another or evidently connected by the importation of the germs, often for great distances, from one place to another. In many places the endemic germ seems to die out until again imported; it retains its vitality for decads.

We have become acquainted with certain conspicuously endemic areas of dengue, especially West India and the eastern coast of Central America, the coast on the Indian Ocean, the Red Sea, and Réunion.

8. The distribution of dengue shows an almost absolute independence of race, nationality, position, and vocation. Earliest childhood, like in influenza, appears to enjoy a relative immunity. The unhygienic, filthy quarters of the densely populated poorer areas and the harbor districts have frequently been the primary foci and principal breeding-places of infection.

SYMPTOMATOLOGY.

The clinical picture of dengue is polymorphic. Quite apart from the great contrast naturally existing between the mildest rudimentary and the most highly developed severe case, there occur also in individual epidemics, at various times and places, marked differences in the clinical picture, differences even in cardinal symptoms—*e. g.*, of the eruption and of the articular affections. Certain influenza epidemics (compare p. 592) were also characterized by such symptomatic variations of type.

Thus some investigators have alleged that intertropical dengue shows semeiotic differences from the extratropical. But it is very likely that some localized epidemics were in earlier times erroneously thought to be dengue. To mention but one example, this was most probably the case with the so-called "dengue fever" that broke out in 1888 upon the ship "Agamemnon" after its departure from Aden.

Nevertheless, dengue in the main shows a specific, exceedingly characteristic picture. We shall now describe the typical course of the fully developed affection. There are two typical stages of the disease, to which a third may be added—the stage of convalescence.

FIRST STAGE (STADIUM FEBRILE).

The disease begins quite suddenly (prodromal symptoms are very rare) with a chill, which frequently develops into a rigor.

Coincidentally with this chill the temperature rises abruptly (more rarely the rise in the temperature is gradual) to 39° or 40° C. or even higher.

Together with this acute onset the other symptoms of the affection appear; they are: severe headache, especially in the frontal region and in the orbits; intense pain in the back, lumbar pains, and especially very characteristic pains in the joints, particularly the knee-joint, making movement an impossibility (hence the name, "abou-rekabe," compare Nomenclature), besides pains in numerous other joints, as of the foot, fingers, hands, and shoulders. Dengue sometimes attacks the limbs so suddenly and painfully that the patient cannot even complete a movement already commenced, so that if kneeling in church, he is unable to arise, or if attacked in the street, he is unable to drag himself home. "Some patients are so stiff from the onset of the affection that they have to be fed. But others, the milder cases, are not compelled to take to bed at all and are able to carry on their usual occupations" (de Brun).

Severe pains in the muscles and a general hyperesthesia of the skin, so that every movement is painful, are frequently noted.

Very characteristic and constant are the gastric symptoms: complete anorexia, a thickly coated tongue (de Brun, Apery, von

Düring), frequently a fetid odor of the mouth, a foul taste, and a tormenting thirst.

Occasionally,—according to von Düring but rarely, and according to other observers frequently,—even in this first *stadium febrile*, a fleeting exanthem ("rash," "eruption premonitoire") appears, which is hardly more than a vasomotor erythema of the skin, especially on the face, where it also may appear in a macular form. The face is reddened, the eyelids are swollen, the conjunctiva is injected, there is photophobia, the pharynx is reddened, the nasal passages are occluded, and even "coryza" has been observed (Smyrna report, von Düring); but all these symptoms, which remind us of influenza, play a minor rôle when compared with the pains in the joints, the gastric symptoms, and the fever, and the strong contrast to influenza lies in the fact that the occurrence of a laryngotracheitis (Hong-Kong, 1895) or a bronchitis (von Düring) is extremely rare.

Very great prostration is always present, and is frequently quite out of proportion to the mildness of the fever and other symptoms.

This first *stadium febrile* usually lasts three days ("three-day fever"). Occasionally, upon the first or second day, but regularly, in the typical cases, upon the third or fourth day, the temperature falls to normal, occasionally by lysis, at other times by crisis, accompanied, in the latter case especially, with profuse perspiration. This really ends the "stadium febrile." It is now that the pathognomonic rash appears and marks the second stage of the disease, the "stadium exanthematis, s. afebrile, subfebrile." Before entering on a description of this stage, some of the more important symptoms may be mentioned more in detail.

The fever rises, as already remarked, after the initial chill, rapidly and considerably, reaching 40° C. and over. Von Düring once observed a temperature of 41.7° C. Very frequently this initial rise of temperature is the highest reached during the whole course of the fever. In mild cases the pyrexia is of but a few hours' duration, and lasts one, two, or, most frequently, in the fully developed cases, three days. In both of the latter cases a progressive, gradual fall of the temperature from day to day is the rule. Only rarely is the three- and four-day fever maintained at a high level (Floras).

If, with the appearance of the rash on the fourth day, a fresh rise of temperature occurs, or if, on the sixth to the eighth day, a relapse, with or without rash, comes on, the temperature-curve naturally assumes the frequently noted recurrent type. The temperature-curve of dengue is remarkably like that of influenza, but in the latter illness the fever plays a far greater part. The fall in temperature on the third or fourth day is generally accompanied by a profuse and, as is stated, very fetid perspiration (Smyrna medical report, de Brun). On the other hand, according to von Düring, the temperature usually falls "without perspiration." But in another place this author speaks of the fetid perspiration occurring toward the termination of the febrile period, and continuing for some time as a symptom of prostration. The onset with high fever frequently causes convulsions in children, and in adults occasionally dizziness and faintness, epileptiform attacks (Shaughter), coma lasting sometimes for a day, but especially delirium, which in the Hong-Kong epidemic of 1895 was frequently observed. Also "maniacal attacks with suicidal tendencies" are mentioned in these initial febrile stages (Mordtmann). The initial delirium and psychoses, rare in dengue, and more frequent in influenza, disappear with the fall of temperature and the appearance of the rash.

There is a considerable difference in the descriptions of the highly characteristic articular pains (especially of the knees) by the physicians of the older and more recent epidemics. The older authors, and among the modern ones Engel-Bey, speak of true articular effusion, of "acute multiple swelling of the joints" quite analogous to rheumatic polyarthritis. These descriptions were naturally used by A. Hirsch and Zülzer. On the other hand, in the later epidemics, de Brun in Smyrna, Mordtmann and von Düring in Constantinople, and Skottowe in the Fiji Islands, never saw inflammation or swelling of the joints; only von Düring speaks of very rare periarticular swellings. According to these authors, there are intra-articular, periarticular, and muscular pains only, which cause the stiffness and the difficulty of movement in the joints. Yet these violent articular pains probably have their origin in hyperemic or inflammatory processes at or in the joints, as indicated by a few post-mortem examinations ("serous infiltration in the vicinity of individual joints, reddening of the crucial ligaments of the knee-joints," quoted from A. Hirsch).

To the already described symptoms in the digestive organs, viz., the pathognomonic anorexia and the thickly coated tongue, may be added nausea, which occurs frequently, and vomiting occasionally. Constipation is the rule. Diarrhea is rare, perhaps principally caused by the purgation method of treatment of dengue, practised in the Orient. Bloody diarrhea, dysenteric manifestations, intestinal hemorrhages, and choleraic diarrhea, such as have been mentioned for influenza, occur only exceptionally in dengue (Mordtmann, von Düring).

According to de Brun, icterus is occasionally present, and von Düring also mentions it once. In the yellow-fever districts of the American tropics the icterus of dengue is said not to be rare (?).

The "pulse" corresponds to the bodily temperature. It is of interest that de Brun has repeatedly observed "marked slowing of the pulse," analogous, therefore, to our observations concerning bradycardia in influenza.

Enlargement of the spleen has, up to now, never been noticed in dengue; its absence is expressly emphasized by von Düring and Sandwith.

Albuminuria is just mentioned by von Düring, and undoubtedly, like in influenza, is only a passing temporary manifestation. There is nowhere any mention of nephritis as a sequel. Nowhere have I found herpes mentioned.

SECOND STAGE (STADIUM EXANTHEMATIS).

Generally on the third or fourth day of the disease the temperature falls to normal and there appears a variable rash. With this begins the second stage of the disease. The rash appears principally on the face, the hands, forearms, and chest; occasionally it spreads over the entire body. It is most frequently described as a scarlatiniform, measly, erysipelatous rash, or as urticaria. A lichen-like exanthem simulating the papular syphilid, an *erythema papulatum multiforme,* is also described. Petechiæ and formation of furuncles are rarely seen (Narich in Smyrna).

In this stage there is not infrequently swelling of the lymphatic glands, particularly those of the neck and groin region (de Brun, von Düring, Narich). Orchitis also is mentioned, and troublesome salivation and parotitis. The rash is often very evanescent, and disappears within a few or after twenty-four hours. In the majority of cases it lasts from two to three days, seldom longer—only exceptionally until the fourteenth day. Occasionally there is a recurrence, particularly on the sixth day, when the rash may reappear as a "miniature edition" of the first (von Düring).

Toward the termination of the rash there arises an extremely intense itching of the skin. This pruritus, with desquamation of the skin, is mentioned by all as a characteristic and very troublesome sequel of dengue. It frequently lasts until the third week, and renders the convalescence more difficult by giving rise to insomnia.

The rash is almost unanimously considered a pathognomonic manifestation of dengue. Kartulis found it constantly, von Düring in nine-tenths of the cases, and Charles and Martialis in two-thirds of the cases. De Brun and the Smyrna medical report say that in exceptional cases the rash may be absent. Morgan asserts that he saw it in only 11 per cent. of the cases. Floras (Constantinople), although he observed in 60 cases the initial cutaneous erythema, the so-called primary rash on the face, on the arms, and trunk, never saw "a completely developed eruption." This may have been a matter of chance. Many secondary exanthemata are of a fleeting nature and easily overlooked (Sandwith), and occasionally recognized only by the succeeding desquamation and pruritus. Many "mild cases," as related by de Brun, "were led to seek medical aid only during the second stage of the disease, by the appearance of the eruption or even after its termination, by the violent itching of the skin."

There is no unanimity of opinion regarding the fever in the *stadium exanthematis.* Many writers emphasize the afebrile stage of the disease at this time; hence the designation, "afebrile" stage. De Brun says: "In some patients the fever declines or disappears at once at the outbreak of the secondary rash; in others, the fever continues or even increases at the occurrence of the eruption." Narich and other Smyrna physicians emphasize the fact that with the appearance of the rash a renewed outbreak of the fever occurs. Von Düring supports this view, especially in regard to rash recurrences, but at the same time, like de Brun, states that the fever of the first stage falls to normal on the fourth day, with the appearance of the eruption. During the exanthematous stage, according to von Düring, there exists "increased normal temperature" or what is otherwise called "subfebrile temperature."

THIRD STAGE (CONVALESCENCE).

After the disease has run its course, which in typical cases is in six to seven days, the stage of convalescence is reached. This is, even after a mild attack, just as in influenza, frequently prolonged by long-continued debility and loss of strength, bodily and mental prostration, insomnia, continuance of gastric disturbances, and often delayed by the persistent itching which accompanies the desquamation. The patients are anemic, have lost flesh, and, according to the Smyrna medical report, "give the impression as if they could recover only with difficulty from a severe prolonged illness." Sandwith and von Düring call attention to marked loss of weight of many dengue patients, in spite of the brevity of their illness (compare the analogous condition in influenza, p. 667). "There is no disease," says de Brun, "which after so brief a duration shows such a debility as dengue." Influenza, at any rate, does the same.

COMPLICATIONS AND SEQUELÆ.

These are, without exception, unusual.

In the first place, certain hemorrhages must be mentioned, which remind us of a similar condition in influenza. While, on the one hand, Skottowe never saw hemorrhages, yet in both the earlier epidemics, also at Smyrna in 1889, they were not quite uncommon, and they were also noticed in Constantinople from time to time. We may mention hemorrhages from the nose, gums, larynx, hematuria, hemorrhages from the bowel, and especially from the stomach. Hematemesis was frequently noted in the epidemic in Madras (1872), sometimes in a pernicious form.

A case of fatal hemorrhage from the stomach is mentioned by Mordtmann. Menorrhagia and metrorrhagia were occasionally seen, but premature births, which especially characterized influenza, were exceedingly rare.

Sequelæ relating to the nervous system are obstinate neuralgias, especially of the trigeminus. Hyperesthesias and anesthesias do not play the part in dengue that they do in influenza. Meningitis as a complication, severe cerebral disturbances, epilepsy, paralyses, paraplegia of the lower extremities, were very uncommon. Sandwith mentions but one case of fatal coma.

The cases of endocarditis and pericarditis observed by de Brun are unquestionably due to mixed infections. Pneumonia and pleurisy practically never occur.

Affections of the eye, apart from conjunctivitis, are exceedingly rare. Keratitis and iritis are mentioned.

Of diseases of the ear, but one case is mentioned: "Bleeding from the ear without otitis."

As sequelæ relating to the joints, long-continued stiffness must be mentioned.

DIAGNOSIS, PROGNOSIS, AND THERAPY.

The **diagnosis** of dengue at the time of an epidemic is very easy. Mild cases, and especially undeveloped cases, can be differentiated from influenza, especially when the latter is complicated by an eruption and respiratory complications are absent, only by the demonstration of the specific influenza bacilli. The diagnosis of dengue need be considered only in the tropical zone and in countries bordering thereon, and of these, chiefly in coast districts. A sudden development of the disease in the interior of a country has never yet been observed with certainty. Endemic dengue is endemic only upon the coast.

The disease may sometimes be mistaken for polyarthritis rheumatica, and especially for the tropical "sun-fever," erythema solare, and may be occasionally confused with erythema exudativum multiforme, which arises epidemically.

Prognosis.—We have already called attention to the exceedingly slight mortality of dengue. Dengue is, in an overwhelming proportion of the cases, a harmless affection.

Among 7435 patients of the English army in India in 1872, only one died. As the highest noted mortality figure, Zülzer gives 0.5 per cent. Von Düring considers the estimated mortality of 1 pro mille in the epidemic of 1889 in Constantinople as too high. In Athens, according to Orenstein, not a single fatal case occurred; in Smyrna, among 100,000 dengue patients, only a few (10) already suffering from chronic disease died (Chrysochoos). Kartulis says the same about Cairo. In the descriptions of the earlier extensive epidemics it is frequently noted that there were no fatal cases. Unquestionably the mortality is exceedingly low compared with the enormous morbidity. Nevertheless, I am convinced that, if in a country in which dengue exists, the mortality statistics were well kept, the occurrence of a dengue epidemic would at once appear from them. Everywhere we find it emphasized that dengue shows a deleterious effect (von Düring and others) upon patients suffering from cardiac affection or tuberculosis, and it is in old, feeble persons and sickly children that complications like hemorrhages from the stomach, enteritis, severe cerebral disturbances carry off one or more persons. No doubt both the direct and the indirect mortality from dengue is much less than from influenza, in which the fatal complication of pneumonia exacts so many victims.

We shall not consider the **therapy** of dengue in any detail. Salicylic acid, antipyrin, and phenacetin have often shown themselves as efficacious sedatives. Quinin, which in the Orient is the favorite drug in all sorts of fevers, and was formerly considered a specific, has, in the judgment of all later observers (de Brun, Apery, Floras, von Düring, Orenstein, and others), proved to be of no effect, and frequently useless, and by many is regarded even as harmful. (Compare section on Therapy of Influenza, p. 694.)

Von Düring says the usual mode of treatment of dengue in the Orient with violent purgatives cannot be too severely condemned.

In a disease which is transmitted almost exclusively by shipping, prophylactic measures, such as quarantine, the prohibiting of the landing from unclean ships, if effectually carried out, may produce the desired result. At the actual locality of the epidemic, measures of prevention, such as isolation and disinfection, have only slight chance of success. Intercourse, commerce, and travel will not allow themselves to be hindered by such a harmless affection.

EPIDEMIOLOGIC AND CLINICAL DIFFERENCES BETWEEN INFLUENZA AND DENGUE.

INFLUENZA.	DENGUE.
Pandemic influenza is distributed equally in all climates, seasons, continents, and seas. Endemic epidemics are more common in the colder season.	Strictly limited to the tropical zone and adjacent districts, occurring particularly in the hot months of the year. Shows special preference for the coasts and shores of rivers, and rarely reaching the interior.
Rapid geographic distribution in all directions.	Slow geographic distribution.
Equally and rapidly distributed over all parts of the affected town.	Often limited to unhygienic quarters.
Acute simultaneous general infection the rule.	The same.
Infectious from person to person. Eminently contagious, perhaps transmitted partly through the air.	Miasmatic contagious (endogenous-exogenous); epidemics dependent upon season and locality.
Duration of pandemic influenza, six to eight weeks; of endemic influenza, often several months.	Duration of epidemic, two to five months.
Independent of race, nationality, social condition, occupation, and sex.	The same.
Relative immunity of early childhood.	The same.

INFLUENZA.	DENGUE.
Immunity generally acquired by an attack.	Probably no acquired immunity.
Enormous morbidity with very slight relative mortality.	The same.
Absolute mortality very considerable. Increase in the general mortality figure by deaths from "acute affections of the respiratory organs" and "pulmonary tuberculosis."	Absolute mortality very slight.
Period of incubation very short—one to a few days.	The same.
Sudden onset without prodromal symptoms, with chill and usually high temperature.	The same.
Average duration of the fever but a few days.	"Three-day fever."
Remittent, intermittent fever-curve, fever relapse. Relapses common.	The same.
Great prostration. Intense pain in the head, loin, back, and extremities.	The same.
Neuralgic joint pains frequent. Inflammation of joints extremely rare.	Extraordinarily intense joint pains, especially of the knee-joints, combined with lightning-like, absolute immobility, often accompanied by inflammatory swelling of the articulations.
Ambulatory form common.	Ambulatory cases rare. Cases compelled to take to bed, the rule.
Catarrhal inflammatory phenomena of the respiratory mucous membrane, coryza, and conjunctivitis, laryngobronchitis, and tracheobronchitis with paroxysmal cough, the rule.	Generally entirely absent.
Pneumonia and pleurisy common. Abscess and gangrene of the lung occasionally.	Almost never.
Severe affection of the nervous system (delirium, coma, epilepsy, and convulsions; encephalitis, meningitis, polyneuritis, myelitis, paralysis, cramps, psychoses, chorea, etc.), not uncommon.	Almost never.
Gastric phenomena not prominent, often absent.	Gastric phenomena—complete anorexia and heavily coated tongue are pathognomonic and prominent symptoms.

INFLUENZA.	DENGUE.
Enteritis hæmorrhagica, dysenteric diarrhea combined with vomiting; bloody flux occasionally.	Hardly ever.
Spleen often enlarged.	Spleen never enlarged (?).
Cardiac asthenia, syncope, angina pectoris, etc., occasionally.	Almost never.
Phlebitis, arterial thrombosis, hemorrhages of all kinds, abortion occasionally.	Almost never.
At the acme of influenza a vasomotor, sometimes macular, reddening of the skin, especially of the face. Genuine eruptions, especially as sequelæ, are very rare.	In the stage of fever a fleeting erythema. On the third to fourth day, a pathognomonic measly-scarlatiniform erysipelatous eruption, with subsequent desquamation and severe pruritus.
Herpes not rare.	Never mentioned.
Otitis frequent.	Never mentioned.
Conjunctivitis, keratitis, neuroretinitis, tenonitis, glaucoma, etc., paralysis of the muscles of the eye, accommodation, etc., repeatedly noted.	Almost never.
Convalescence in the majority of cases prompt and of brief duration; occasionally, however, protracted.	Convalescence usually very protracted.

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